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(54) Title: METHODS OF TREATMENT AND COMPOSITIONS FOR USE THEREOF

(57) Abstract: The present invention is directed to a method of treating or preventing pain in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment or prevention a μ -opioid agonist and levorphanol, wherein said concurrent administration produces an enhanced effect. The present invention is also directed to pharmaceutical compositions comprising a μ -opioid agonist and levorphanol useful for carrying out the method of the present invention.

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METHODS OF TREATMENT AND COMPOSITIONS FOR USE THEREOF

[0001] The application claims the benefit of U.S. Provisional Application No. 60/694,975, filed June 30, 2005, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention is in the field of pharmaceutical compositions and the use thereof for treating and preventing pain.

BACKGROUND ART

[0003] Currently, medical practitioners may choose from several well-accepted classes of pharmaceutical agents in their attempts to alleviate and prevent pain. Nonlimiting examples of agents used include nonsteroidal anti-inflammatory agents (NSAIDs), *e.g.*, aspirin, ibuprofen, ketoprofen, diclofenac; opioids, *e.g.*, morphine, hydromorphone, hydrocodone, oxycodone, tramadol, and codeine; cyclooxygenase-2 (COX-2) selective NSAIDs, *e.g.*, celecoxib, valdecoxib, etoricoxib, lumiracoxib, and rofecoxib; acetaminophen; tricyclic antidepressants, *e.g.*, amitriptyline, desipramine, nortriptyline; non-tricyclic antidepressants, *e.g.*, doxepin, duloxetine, paroxetine, venlafaxine; antiepileptics, *e.g.*, gabapentin, pregabalin, carbamazepine, oxcarbazepine, lamotrigine; voltage sensitive N-type calcium channel blockers, *e.g.*, ziconotide and alpha adrenergic agonists, *e.g.*, clonidine.

[0004] Of the many challenges that occur when pharmacologically treating any disease or pathological condition, including pain, alleviating the symptoms without causing counterproductive side effects is often the greatest. This challenge presents itself when medical practitioners use medicinal agents to treat

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pain. Although the aforementioned pharmacological classes are frequently effective for the treatment of certain types of pain, the chronic and acute use of these analgesic agents produces a number of significant, undesirable side effects.

[0005] Morphine is extensively utilized for the management of severe pain due to its global availability, extensive clinical experience, significant pharmacokinetic and pharmacodynamic data, low cost and the availability of various extended release formulations (Babul et. al, J Clin Pharmacol, 1998;38:74-81). However, the incidence and severity of side effects limits the use of morphine in some patients (Hagen and Babul, Cancer 1997;79:1428-37). In patients with renal impairment, morphine's principal metabolites, morphine-3-glucuronide and morphine-6-glucuronide can accumulate. Morphine-3-glucuronide accumulation has been implicated in hyperalgesia, respiratory stimulation, and behavioral excitatory properties through nonopioid receptor mechanisms. Morphine-6-glucuronide accumulation has been implicated in increasing levels of nausea and sedation in patients with renal impairment (Babul and Darke, Clin Pharm Ther, 1993;54:286-92). Similarly, the principal metabolite of hydromorphone, hydromorphone-3-glucuronide can accumulate in patients with renal impairment and has been found to be more neurotoxic than morphine-3-glucuronide (Babul and Darke, Pain, 1992;51:260-61; Hagen et al., J Clin Pharmacol, 1995;35:38-45; Babul et al., J Pain Symptom Manage, 1995;10:184-86; Wright et al., Life Sci, 1998;63:401-11; Wright et al., Life Sci, 2001;69:409-20.).

[0006] There are now many compounds with pharmacological properties similar to those produced by morphine. Although there can be striking variability in response to opioids in an individual patient, none of the commercially available opioids have proven to be clinically superior to morphine in relieving pain when used at equianalgesic doses in carefully controlled clinical trials. Non-limiting examples of morphine-like opioids include alfentanil, carfentanil, diamorphine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, lofentanil, meperidine, oxycodone, oxymorphone, remifentanil and sufentanil.

[0007] Unlike doses of non-opioid analgesics, partial opioid agonists and mixed opioid agonist-antagonists, pure or full opioid agonists such as morphine, hydromorphone, oxycodone, fentanyl, carfentanil, lofentanil, alfentanil and sufentanil do not have a “dose ceiling”. In other words, their doses can be increased almost indefinitely, being limited only by the occurrence of side effects.

[0008] Among the many side effects of opioids are nausea, vomiting, constipation, sedation, fatigue, pruritus, blurred vision, urinary retention, respiratory depression, convulsions, mood changes and alterations of the endocrine and autonomic nervous systems. Many of these side effects are sufficiently bothersome as to require: i) use of additional medications to treat the iatrogenic symptoms; ii) more intensive patient management; iii) use of lower doses that leave patients in continued pain; or iv) in other cases, complete discontinuation of analgesic therapy. Opioids can also produce potentially fatal respiratory depression at high doses. (Evidence Based Report of the U.S. Agency for Healthcare Research and Quality (AHRQ) on the Management of Cancer Pain, Report No. 35, AHRQ Publication No. 02-E002, October 2001; Carr et al. J Nat Cancer Inst Monograph 2004;32:23-31; Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, March 1994; Guideline for the Management of Cancer Pain in Adults, American Pain Society, 2005).

[0009] Undertreatment of pain may also occur when higher doses of opioid analgesics are required to manage the patient’s pain due to: 1) prescribing resistance by clinicians and 2) patient and family barriers to dose escalation. Physicians frequently have exaggerated fears about the risk of iatrogenic addiction, respiratory depression and the risk of adverse regulatory sanctions. Similarly, patients and family members have fears about drug addiction and in some cases, equating increased opioid requirement with terminal disease, death and dying.

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- [0010] Opioids exert effects on the neuroendocrine system, including hypothalamic inhibition of the release of gonadotropin releasing hormone and corticotropin-releasing factor, thereby decreasing circulating concentrations of luteinizing hormone, follicle stimulating hormone, adrenocorticotropin and β -endorphin. As a result of the decreased concentrations of pituitary trophic hormones, plasma concentrations of testosterone and cortisol decline. The administration of opioids increases plasma prolactin concentrations, most likely by reducing the dopaminergic inhibition of prolactin secretion.
- [0011] Opioid side effects are managed by: i) adjusting the dose; ii) adding a non-analgesic drug to manage side effects (e.g., a laxative or antiemetic); iii) switching to another opioid; iv) using a non-opioid analgesic or iv) using suboptimal opioid doses that provide only partial pain relief.
- [0012] In some patients, no intervention is effective in attaining an optimal balance between analgesia and acceptable side effects. For this reason, there has been an ongoing but so far unsuccessful effort to develop opioids with a superior side effect profile than currently available opioids.
- [0013] An alternative strategy to provide optimal analgesia without intolerable side effects has involved use of lower doses of an opioid analgesic in combination with one or more non-opioid drugs, thereby reducing the side effects that might otherwise occur from higher opioid doses given alone.
- [0014] Reference may be made to U.S. Patent No. 2,770,569 which is directed to a combination of the opioid antagonist levo-3-hydroxy-N-allyl-morphinan with various opioid agonists, including alphaprodine, desomorphine, levorphanol, meperidine and morphine, which is aimed reducing the side effects of opioid agonists.
- [0015] Reference also may be made to U.S. Patent No. 4,126,684 which discloses a method of reducing the addiction liability or withdrawal symptoms in patients receiving an opioid or barbiturate by administering 4-amino-3-p-halophenylbutyric acids.

- [0016] Reference also may be made to U.S. Patent No. 4,487,252 which discloses a method for providing enhanced analgesic effects by co-administering hydrocodone and ibuprofen.
- [0017] Reference may be made to U.S. Patent No. 4,569,937 which is directed to pharmaceutical compositions of ibuprofen and the opioid analgesic oxycodone which exhibit synergism enabling the use of lower doses of either or both drugs with a concomitant reduction in risk of possible side effects.
- [0018] Reference also may be made to U.S. Patent No. 4,769,372 which describes a method for treating chronic pain in a patient while preventing or alleviating the development of constipation or other symptoms of intestinal hypomotility wherein the opioid analgesic morphine, meperidine, oxycodone, hydromorphone, codeine and hydrocodone is administered together with an opioid antagonist such as naloxone and nalmefene.
- [0019] Reference may also be made to U.S. Patent No. 5,041,446 which discloses a method of inhibiting the development of tolerance to morphine by coadministering it with dapiprazole.
- [0020] Reference may also be made to U.S. Patent No. 5,057,519 which discloses a method for delaying the onset of opioid tolerance by coadministration of a benzamide-type 5-HT₃ antagonist.
- [0021] Reference also may be made to U.S. Patent No. 5,317,022 which describes a composition for the selective blockade of CNS opioid binding sites responsible for respiratory depression while maintaining analgesia, comprising an analgesic effective amount of a codeinone derivative and in a mass ratio of 1:2-3 morphine or a morphine derivative indicated therein.
- [0022] Reference may also be made to U.S. Patent No. 5,336,691 which discloses a method of treating pain comprising co-administration of tramadol and acetaminophen, said composition and method providing synergistic effects with less opioid side-effects.

- [0023] Reference also may be made to U.S. Patent No. 5,512,578 which is directed to a method for selectively enhancing the analgesic potency (inhibitory effects) of a bimodally acting opioid agonist such as morphine and simultaneously attenuating the development of physical dependence, tolerance and other undesirable side effects caused by chronic administration thereof, comprising co-administration of a bimodally acting opioid agonist and an opioid receptor antagonist which selectively inactivates excitatory opioid receptor-mediated side effects.
- [0024] Reference may also be made to U.S. Patent No. 5,919,826 which discloses a method of alleviating pain which comprises administering the opioid agonist tramadol and a tramadol analgesia-enhancing, but essentially subanalgesic dose of the NMDA antagonist's dextromethorphan or dextrorphan.
- [0025] Reference may also be made to U.S. Patent No. 6,007,841 which discloses an analgesic composition comprising a narcotic agonist-antagonist analgesic selected from the group consisting of pentazocine, nalbuphine, butorphanol, buprenorphine, meptazinol, dezocine, nalorphine, cyclazocine and an NMDA receptor antagonist.
- [0026] Reference also may be made to U.S. Patent Application No. 10/824,357 which describes a method of treating or preventing pain comprising administering a μ , κ or δ opioid receptor agonist and a beta adrenergic agonist wherein the beta adrenergic agonist produces an enhanced effect of the μ , κ or δ opioid receptor agonist.
- [0027] Reference also may be made to U.S. Patent No. 6,310,072 which describes an analgesic composition comprising a subanalgesic dosage of a μ -opioid agonist selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil and hydromorphone, or a pharmaceutically acceptable salt thereof, and a subanalgesic dosage of oxycodone which is a putative κ_2 opioid agonist, said compositions having a higher analgesic potency and lower propensity for causing side effects.

[0028] It is a commonly held view that all clinically used opioid drugs including alfentanil, fentanyl, lofentanil, carfentanil, remifentanil, hydromorphone, levorphanol and oxycodone mediate their analgesic and antinociceptive effects in the same manner as morphine, namely through interactions of μ -opioid receptors in the CNS.

[0029] The μ -opioid receptor mediates the actions of morphine and morphine-like opioids, including most clinical analgesics. In addition to morphine, several highly selective agonists have been developed for μ -opioid receptors, including [D-Ala²,MePhe⁴,Gly(ol)⁵] enkephalin (DAMGO), etorphine, fentanyl, sufentanil, bremazocine and methadone. Among the μ -opioid receptor antagonists are naloxone, naltrexone, D-Phe-Cys-Trp-D-Trp-Orn-Thr-PenThr-NH₂ (CTOP), diprenorphine, (3-funaltrexamine, naloxonazine, nalorphine, nalbuphine, and naloxone benzoylhydrazone. Differential sensitivity to antagonists, such as naloxonazine, indicates the pharmacologic distinctions between the mu-opioid receptor subtypes, μ_1 and μ_2 . Several of the opioid peptides also interact with mu-opioid receptors.

[0030] The δ -opioid receptors are divided into two subclasses, δ_1 , and δ_2 . The δ -opioid receptors modulate analgesia through both spinal and supraspinal pathways. The two subclasses were proposed based on their differential sensitivity to blockade by several novel antagonists (Portoghese et al. (1992) Eur. J. Pharmacol. 218:195; and Sofuoglu et al. (1991) J. Pharmacol. Ther. 257:676). The agonists [D-Pro²,Glu⁴] deltorphin and [D-Ser²,Leu⁵] enkephalin-Thr⁶ (DSLET) preferentially bind to the δ_2 receptors, whereas [D-Pen²,D-Pen⁵] enkephalin (DPDPE) has a higher affinity for δ_1 receptors.

[0031] The κ -opioid receptor was initially defined in binding studies using drugs such as U50,488H and nor-binaltorphimine (norBNI). The κ_2 -opioid receptor differs from the κ_1 -opioid receptor in terms of the binding selectivity. Another kappa receptor subtype was identified which subtype is unique. Like the κ_2 -opioid receptor, the κ_3 -opioid receptors (Clark, et al. (1989), Price, et al.

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(1988), Gistrak, et al. (1989), and Paul, et al. (1989)) do not bind U50,488H or nor-binaltorphimine very well. The overall binding selectivity of κ_3 -opioid receptors is quite different from that of the κ_2 -opioid receptor as well as that of any other published receptor class (Tive et al., *Neuropharmacol*, 1992;31:851-56). In addition to the unique binding profile, the κ_3 -opioid receptors have a novel and distinctive pharmacology. Using a novel ligand, naloxone benzoylhydrazone (NalBzoH), the ability of κ_3 -opioid receptors to elicit analgesia has been confirmed. This κ_3 analgesia does not appear to be associated with respiratory depression or significant constipation. In this regard, the κ_3 analgesia is quite distinct from the actions of morphine. Furthermore, antagonists which selectively block μ , δ , κ_1 and κ_2 analgesia have little effect on κ_3 analgesia (Tive et al., *Neuropharmacol*, 1992;31:851-56). In summary, there are three known κ -opioid receptor subtypes, designated κ_1 , κ_2 and κ_3 . Each κ -opioid receptor subtype possesses distinct pharmacologic properties. For example, κ_1 -opioid receptors produce analgesia spinally and κ_3 -opioid receptors relieve pain through supraspinal mechanisms. In addition, the κ_1 -opioid receptor selectively binds to the agonist U50,488. Additional agonists of the κ_1 -opioid receptor include etorphine; sufentanil; butorphanol; (3-funaltrexamine; nalphorine; pentazocine; nalbuphine; bremazocine; ethylketocyclazocine; U50,488; U69,593; spiradoline; and nor-binaltorphimine. Agonists of the κ_3 -opioid receptor include etorphine; levorphanol; naloxone benzoylhydrazone; bremazocine; and ethylketocyclazocine. Effects of agonists on the κ_1 -opioid receptors are reversed by a number of antagonists, including buprenorphine, naloxone, naltrexone, diprenorphine, naloxonazine, naloxone benzoylhydrazone, naltrindole and nor-binaltorphimine. Antagonists of the κ_3 -opioid receptors include naloxone, naltrexone and diprenorphine.

[0032] Recent years have seen the development of novel opioid analgesics acting through receptors distinct from those utilized by morphine. It has been suggested that since the effects of endogenous opioids are mediated by at least these

three different receptor types, highly selective exogenous opioid agonist or antagonist ligands might have therapeutic applications (Martin, W. R., 25 1983, Pharmacol. Rev., 35, 283). Thus, if a ligand acts at a single opioid receptor type or sub-type, the potential side effects mediated through other opioid receptor types can potentially be minimized or eliminated. In this regard, reference may be made to U.S. Patent No. 5,352,680 which is directed to a therapeutic method for treating opioid tolerance comprising administering a δ -opioid receptor antagonist to reduce the tolerance of μ -opioid receptor agonist such as morphine.

[0033] Reference also may be made to U.S. Patent No. 5,319,087 which discloses the blocking of the μ or κ -opioid receptors in the brain using trans-3,4-1-substituted-3-substituted-4-methyl-4-(3-substituted phenyl)-piperidines as opioid antagonists.

[0034] Several studies have demonstrated that combinations of μ and δ opioid receptor agonists, administered spinally, produce enhanced analgesic effects (Larson *et al.*, 1980, Eur. J. Pharmacol., 61, 381-383; Roerig & Fugimoto, 1989, J. Pharmacol. Exp. Ther. 249, 762-768). Other studies have shown that simultaneous spinal administration of combinations of a selective μ -opioid agonist (DAMGO) with both a κ_1 -selective (U50,488H) or a δ -selective (DPDPE) opioid receptor agonist also produce analgesic synergy (Miaskowski *et al.*, 1990, Brain Research, 509, 165-168). In addition, potent analgesic synergy has been observed with combinations of a low analgesic dose of a selective μ -agonist (DAMGO) co-administered into the CNS with sequentially increasing doses of either a selective δ -(DPDPE) or a selective κ_1 -opioid receptor agonist (U50,488H) (Sutters *et al.*, 1990, Brain Research, 530, 290-294). Co-administration of sub-antinociceptive doses of the putative κ_2 -opioid receptor agonist oxycodone and the μ -opioid receptor agonist morphine demonstrates synergistic antinociception (Ross FB *et al.*, Pain 2000;84:421-28).

[0035] These studies demonstrate that all three major classes of opioid receptors can interact to produce antinociceptive synergy. However, the magnitude of the interactions vary markedly depending on which combinations of selective opioid receptor agonists are administered. The data from these studies demonstrate that coactivation of the μ -opioid receptor agonist, with either δ , κ_1 - or κ_2 -opioid receptor agonist, results in the largest enhancement in antinociceptive effects.

[0036] From the foregoing, a number of non-toxic substances have been defined which may ameliorate some of the undesirable side effects resulting from prolonged administration of strong opioids. In addition, combinations of experimental substances have been defined including μ , δ , κ_1 , κ_2 -agonists which result in a synergistic increase in analgesia.

[0037] With the exception of U.S. Patent No. 6,310,072 which describes the co-administration of subanalgesic dosages of a μ -opioid agonist selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil and hydromorphone and a subanalgesic dosage of the putative κ_2 opioid receptor agonist, oxycodone, the art does not suggest in any way the desirability of concurrent administration of two strong opioids for analgesic synergy and/or amelioration of their respective undesirable side effects. More specifically, the art does not suggest in any way either: 1) the desirability of either the co-administration of two μ -opioid receptor agonists (the so called "full agonists" or "strong analgesics") or 2) the concurrent administration of a μ -opioid receptor agonists (the so called "full agonists" or "strong analgesics") with levorphanol, a putative κ_3 -opioid receptor agonist, or any other κ_3 -opioid receptor agonist. In fact, just the opposite is suggested. For example, in the World Health Organization's (WHO) guidelines for the relief of cancer pain (Cancer Pain Relief, 2nd Ed., 1996, pp.15-16), it is recommended that co-administration of two strong opioids should never be attempted. Instead, it is recommended that an analgesic ladder should be followed wherein a non-opioid drug is administered initially to a patient and when pain persists or increases, a weak opioid is added to the medication. When the weak opioid

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drug in combination with the non-opioid drug fails to relieve the pain, a strong opioid is then administered in place of the weak opioid drug. Importantly, it is stipulated that only one opioid drug should be given at any one time.

[0038] The Evidence Based Report of the U.S. Agency for Healthcare Research and Quality (AHRQ) on the Management of Cancer Pain (Report No. 35, AHRQ Publication No. 02-E002, October 2001; Carr et al. J Nat Cancer Inst Monograph 2004;32:23-31) supports the three tier approach. "The first tier, for mild to moderate pain, consists of NSAIDs and acetaminophen with or without adjuvant medications. As pain escalates or persists, treatment progresses to the second tier, in which a weak opioid, such as codeine or hydrocodone, is added to the NSAID with or without an adjuvant drug." "If pain still persists, treatment progresses to the third tier: substitution of the "weak" opioid for a "strong" opioid (i.e., one more readily titrated to doses with greater analgesic efficacy). The latter category includes morphine, hydromorphone, methadone, fentanyl, and levorphanol, all full opioid agonists at the morphine or mu receptor." The AHRQ report further notes that "if pain relief is not achieved at the maximum recommended dose of a particular NSAID or opioid, it should be discontinued and another drug from the same class tried before abandoning that class. Case series indicate that on an individual basis, other drugs from the same class may prove more effective or be better tolerated." There is no suggestion on the concurrent use of μ -opioid receptor agonists with levorphanol, a putative κ_3 -opioid receptor agonist, or any other κ_3 -opioid receptor agonist.

[0039] The Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management (Guideline No. 9, AHCPR Publication No. 94-0592, March 1994) states: "It is usually advisable to observe the patient's response to several different opioids, sequentially, before switching routes of administration or trying an anesthetic, neurosurgical, or other invasive approach to relieve persistent pain. For example, patients who experience dose-limiting sedation, nausea, or mental clouding on oral morphine should be switched to an

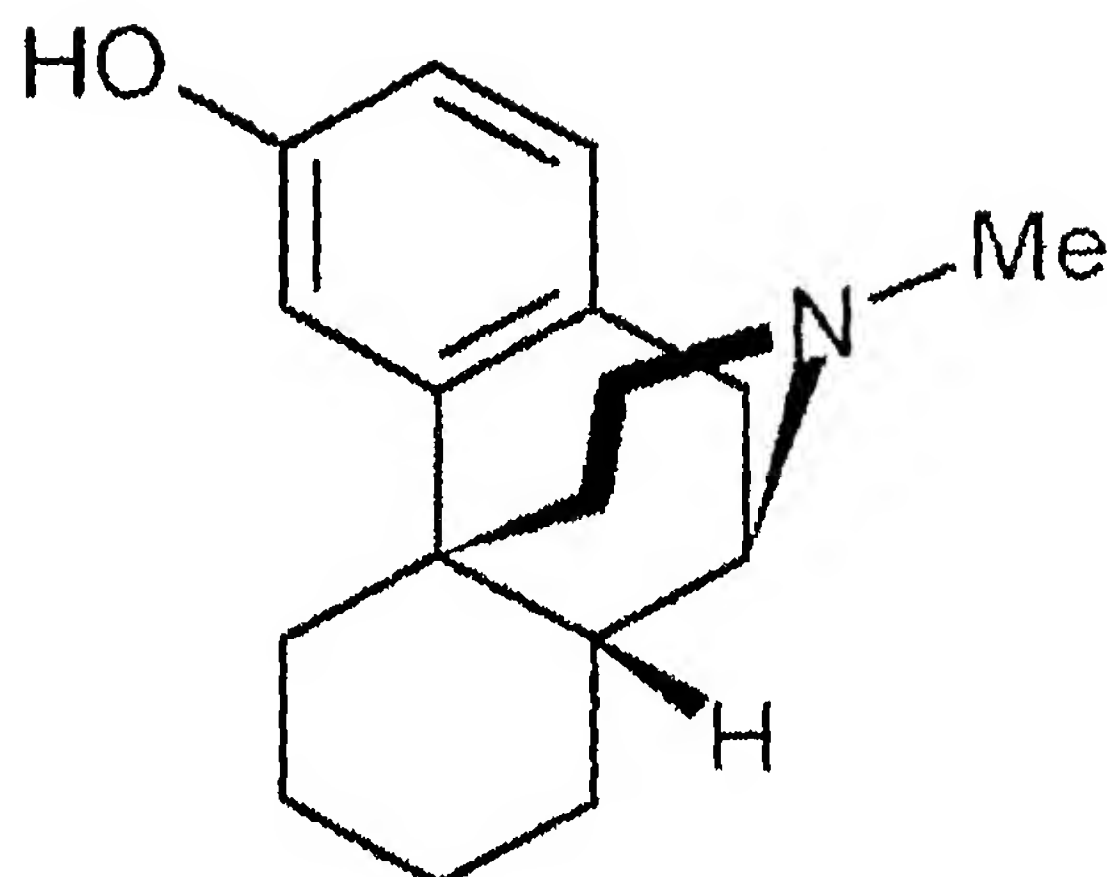
equianalgesic dose of hydromorphone or fentanyl. The dose of the second opioid should then be adjusted. Sequential analgesic trials should be based on regular assessments of pain, with continuous attention to antineoplastic and noninvasive nonpharmacologic therapies". There is no reference to the concurrent use of μ -opioid receptor agonists with levorphanol, a putative κ_3 -opioid receptor agonist, or any other κ_3 -opioid receptor agonist.

[0040] According to the European Association of Palliative Care Expert Working Group on Opioids (Hanks et al, British Journal of Cancer 2001; 84: 587–593), "none of the alternatives to morphine has so far demonstrated advantages which would make it preferable as the first line oral opioid for cancer pain."

[0041] According to the recently issued American Pain Society Guideline for the Management of Cancer Pain in Adults (2005, pp.59-60), "For patients who experience inadequate pain relief, or an unacceptable level of side effects from a specific opioid that limits dose escalation, pain control can be achieved through opioid rotations. For example, patients who experience dose-limiting sedation, nausea, or mental clouding from oral morphine can be switched to an equianalgesic dose of hydromorphone or fentanyl. Dosage of the second opioid should then be adjusted so that relief is achieved with an acceptable level of side effects. It is usually advisable to observe a patient's response to several different opioids, administered sequentially, before switching routes of administration or trying an anesthetic, neurosurgical, or other invasive approach to relieve persistent cancer pain". There is no reference to the concurrent use of more than one opioid to treat acute or chronic pain.

[0042] Levorphanol tartrate dihydrate is a potent narcotic analgesic with a molecular formula of $C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot 2H_2O$ and molecular weight 443.5. Levorphanol's chemical name is levo-3-hydroxy-N-methylmorphinan with the following structural formula, and has 3 asymmetric carbon atoms and the possibility of cis-trans isomerism:

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[0043] Levorphanol is widely considered to be an alternative to morphine and other strong opioid agonists in patients with moderate to severe acute and chronic pain. There are no data or suggestions in the literature or in clinical practice that levorphanol has efficacy superior to any other strong opioid analgesic or that it should be co-administered with other strong opioid analgesics at analgesic or subanalgesic doses. Indeed, leading reference sources in pain management indicate that at equipotent or equianalgesic doses, levorphanol produces analgesia comparable to morphine, oxycodone, hydromorphone, fentanyl and other strong opioids (Guideline for the Management of Cancer Pain in Adults, American Pain Society, 2005; Clinical Practice Guidelines for Cancer Pain Management, Agency for Health Care Policy and Research Guideline No. 9, AHCPR Publication No. 94-0592, March 1994).

[0044] Levorphanol has demonstrated efficacy and safety in acute and chronic pain (FDA Approved Prescribing Information, Roxane Laboratories, Inc. December 2004) and in neuropathic pain (Rowbotham, N Engl J Med 2003;348:1223-32).

[0045] Without being bound by theory, the current invention arises from the unexpected discovery that co-administration of subanalgesic dosages of μ -opioid receptor agonists and levorphanol, a putative κ_3 -opioid receptor agonist results in potent analgesic synergy and a reduced propensity for causing the

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undesirable side effects herein described. Nonlimiting examples of μ -opioid receptor agonists include alfentanil, alphaprodine, anileridine, buprenorphine, butorphanol, carfentanil, codeine, dezocine, dextromoramide, diamorphine, dihydrocodeine, dihydrocodeinone, dihydromorphine, fentanyl, hydrocodone, hydromorphone, levomethadone, lofentanil, meperidine, meptazinol, methadone, morphine, nalbuphine, normethadone, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, propiram, propoxyphene, remifentanil, sufentanil and tramadol and their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates, as a racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.

BRIEF SUMMARY OF THE INVENTION

[0046] Surprisingly, μ -opioid receptor agonists including alfentanil, alphaprodine, anileridine, buprenorphine, butorphanol, carfentanil, codeine, dezocine, dextromoramide, diamorphine, dihydrocodeine, dihydrocodeinone, dihydromorphine, fentanyl, hydrocodone, hydromorphone, levomethadone, lofentanil, meperidine, meptazinol, methadone, morphine, nalbuphine, normethadone, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, propiram, propoxyphene, remifentanil, sufentanil and tramadol can be advantageously used together with levorphanol, a putative κ_3 -opioid receptor agonist, and administered to subjects to not only elicit a more potent analgesic response but also to evoke such response more rapidly and/or for longer duration and with fewer side effects than possible by administration of the μ -opioid receptor agonists alone.

[0047] A first aspect of the present invention is directed to a novel method for eliciting a greater analgesic response, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.

- [0048] A second aspect of the present invention is directed to a novel method for eliciting a faster analgesic response, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0049] A third aspect of the present invention is directed to a novel method for increasing the duration of analgesic response, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0050] A fourth aspect of the present invention is directed to a novel method for increasing the peak analgesic response, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0051] A fifth aspect of the present invention is directed to a novel method for reducing the propensity for causing undesirable opioid side effects, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0052] A sixth aspect of the present invention is directed to novel pharmaceutical compositions of matter for use in enhancing the onset, peak, duration and overall magnitude of analgesic effect in acute and chronic pain, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0053] A seventh aspect of the present invention is directed to novel pharmaceutical compositions of matter for use in for reducing the propensity for causing undesirable opioid side effects in acute and chronic pain, said method comprising administering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0054] An eighth aspect of the present invention is directed to a novel method for eliciting a greater analgesic response, said method comprising administering an

analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0055] A ninth aspect of the present invention is directed to a novel method for eliciting a faster analgesic response, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0056] A tenth aspect of the present invention is directed to a novel method for increasing the duration of analgesic response, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0057] A eleventh aspect of the present invention is directed to a novel method for increasing the peak analgesic response, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0058] A twelfth aspect of the present invention is directed to a novel method for reducing the propensity for causing undesirable opioid side effects, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0059] A thirteenth aspect of the present invention is directed to novel pharmaceutical compositions of matter for use in enhancing the onset, peak, duration and overall magnitude of analgesic effect in acute and chronic pain, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

[0060] A fourteenth aspect of the present invention is directed to novel pharmaceutical compositions of matter for use in for reducing the propensity for causing undesirable opioid side effects in acute and chronic pain, said method comprising administering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

DETAILED DESCRIPTION OF THE INVENTION

- [0061] The present invention provides a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention a subanalgesic dose of a μ -opioid receptor agonist and a subanalgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist.
- [0062] The present invention also provides a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention an analgesic dose of a μ -opioid receptor agonist and a subanalgesic or analgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist.
- [0063] In one embodiment, a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol are administered to provide an enhanced analgesic response.
- [0064] In one embodiment of the present invention, "enhanced analgesic response" means that, when coadministered with levorphanol, lower doses of the selected μ -opioid receptor agonist are required to achieve the same analgesic effect as when the μ -opioid receptor agonist is administered alone or greater analgesic effect is achieved when usual doses of the selected μ -opioid receptor agonist are administered with levorphanol.
- [0065] The invention also provides a method for eliciting a faster analgesic response by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0066] The invention also provides a method for increasing the duration of analgesic response by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0067] The invention also provides a method for increasing the peak analgesic response by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.

- [0068] The invention also provides a method for reducing the propensity for causing undesirable opioid side effect by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0069] The invention also provides for pharmaceutical compositions of matter for use in enhancing the onset, peak, duration and overall magnitude of analgesic effect in acute and chronic pain by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0070] The invention also provides for pharmaceutical compositions of matter for use in for reducing the propensity for causing undesirable opioid side effects in acute and chronic pain by coadministering a subanalgesic amount of a μ -opioid receptor agonist and a subanalgesic amount of levorphanol.
- [0071] The invention also provides a method for enhancing the analgesic effect when levorphanol is administered as rescue analgesics in patients experiencing breakthrough pain while receiving around-the-clock, scheduled or intermittent treatment with μ -opioid receptor agonists.
- [0072] The invention also provides for pharmaceutical compositions of matter for use in enhancing the analgesic effects when levorphanol is administered intermittently to treat breakthrough pain in patients receiving ongoing or baseline therapy with subanalgesic doses of a μ -opioid receptor agonist.
- [0073] In one embodiment, a subanalgesic amount of levorphanol is administered to treat breakthrough pain in subjects receiving μ -opioid receptor agonists. In another embodiment, an analgesic amount of levorphanol is administered to treat breakthrough pain in subjects receiving μ -opioid receptor agonists.
- [0074] The invention also provides a method for eliciting a faster analgesic response by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or or analgesic amount of levorphanol.
- [0075] The invention also provides a method for increasing the duration of analgesic response by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.

- [0076] The invention also provides a method for increasing the peak analgesic response by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.
- [0077] The invention also provides a method for reducing the propensity for causing undesirable opioid side effect by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.
- [0078] The invention also provides a method for enhancing the onset, peak, duration and overall magnitude of analgesic effect when subanalgesic or analgesic doses of levorphanol are administered intermittently to treat breakthrough pain in patients receiving ongoing or baseline therapy with analgesic doses of a μ -opioid receptor agonist.
- [0079] The invention also provides a method for enhancing the onset, peak, duration and overall magnitude of analgesic effect when subanalgesic or analgesic doses of levorphanol are administered as rescue analgesics in patients experiencing breakthrough pain while receiving around-the-clock, scheduled or intermittent treatment with analgesic doses of a μ -opioid receptor agonist.
- [0080] The invention also provides for pharmaceutical compositions of matter for use in enhancing the onset, peak, duration and overall magnitude of analgesic effect in acute and chronic pain by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.
- [0081] The invention also provides for pharmaceutical compositions of matter for use in for reducing the propensity for causing undesirable opioid side effects in acute and chronic pain by coadministering an analgesic amount of a μ -opioid receptor agonist and a subanalgesic or analgesic amount of levorphanol.
- [0082] The invention also provides for pharmaceutical compositions of matter for use in enhancing the analgesic effects when subanalgesic or analgesic doses of levorphanol are administered intermittently to treat breakthrough pain in patients

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receiving ongoing or baseline therapy with analgesic doses of a μ -opioid receptor agonist.

[0083] "Drug," "pharmacological agent," "pharmaceutical agent," "active agent,"

and "agent" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial effect. In general, this includes therapeutic agents in all of the major therapeutic areas, also including proteins, peptides, oligonucleotides, and carbohydrates as well as inorganic ions, such as sodium ion, calcium ion, lanthanum ion, potassium ion, magnesium ion, phosphate ion, and chloride ion.

[0084] "Pharmaceutically or therapeutically acceptable excipient or carrier" refers to a solid or liquid filler, diluent or encapsulating substance which does not interfere with the effectiveness or the biological activity of the active ingredients and which is not toxic to the hosts, which may be either humans or animals, to which it is administered. Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well known in the art may be used. Nonlimiting examples are sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

[0085] The term "subject" for purposes of treatment is used interchangeably with "patient", "male", "female", "rat" and "animal", and includes any animal subject who has any one of the known forms of pain. The subject is preferably a mammal and more preferably is a human.

[0086] As used herein, "equianalgesic doses," also referred to as "analgesic equivalence," is a term used by practitioners of the art to refer to approximately comparable doses of analgesics required to provide a similar magnitude of analgesia. There are established standards to allow practitioners of the art to convert the dose of one analgesic, given by any route of administration, to an

approximately equivalent dose of another analgesic, given by any route of administration. These analgesic conversion tables provide what in the art is called “analgesic equivalence” or “equianalgesic doses”. Similarly, to allow for comparisons of doses involving opioids with varying analgesic potencies, pain physicians and clinical investigators convert the doses of various opioids given by a specific route of administration to morphine and express the doses in “morphine analgesic equivalents”. In a variation of this example, opioid doses involving different routes of administration may be converted to equivalent doses by a specific route of administration. By way of a non-limiting example, if intravenous hydromorphone is considered to five times as potent as oral hydromorphone, a 6 mg dose of intravenous hydromorphone may be expressed as “equivalent to 30 mg of oral hydromorphone”. (Guideline for the Management of Cancer Pain in Adults, American Pain Society, 2005; Clinical Practice Guidelines for Cancer Pain Management, Agency for Health Care Policy and Research Guideline No. 9, AHCPR Publication No. 94-0592, March 1994.). The availability of analgesic equivalence tables allows practitioners of the art to convert patients from one analgesic to another without a protracted titration period on the new analgesic. It is well known to practitioners of the art that where a direct comparison of equianalgesia between two opioids is not available, several methods are used to determine equianalgesic doses, including: 1) comparison with a third opioid; 2) comparative evaluation of antinociceptive effects in established preclinical pain models, including those referred herein.

[0087] Dose Equivalents for Opioid Analgesics in Opioid-Naïve Adults and Children \geq 50 kg Body Weight

Drug	Approximate equianalgesic dose		Usual starting dose for moderate to severe pain	
	Oral	Parenteral	Oral	Parenteral
Opioid agonist				
Morphine	30 mg q 3-4 h (repeat around-the-clock dosing) 60 mg q 3-4 h (single dose or intermittent dosing)	10 mg q 3-4 h	30 mg q 3-4 h	10 mg q 3-4 h
Morphine, 12 hr controlled-release (MS Contin™)	90-120 mg q 12 h	N/A	90-120 mg q 12 h	N/A
Oxycodone	10 to 30 mg q 4-6h	N/A		N/A
Oxycodone 12 hr controlled-release (OxyContin™)	40 to 60 mg q 12h	N/A	20 to 40 mg q 12h	N/A
Hydromorphone (Dilaudid™)	7.5 mg q 3-4 h	1.5 mg q 3-4 h	6 mg q 3-4 h	1.5 mg q 3-4 h
Levorphanol (Levo-Dromoran™)	4 mg q 6-8 h	2 mg q 6-8 h	4 mg q 6-8 h	2 mg q 6-8 h
Meperidine (Demerol™)	300mg q 2-3 h	100 mg q 3 h	N/R	100 mg q 3 h
Methadone (Dolophine™, other)	20 mg q 6-8 h	10 mg q 6-8 h	20 mg q 6-8 h	10 mg q 6-8 h
Oxymorphone (Numorphan)	5 to 15 mg q 4-6 h	1 mg q 3-4 h	N/A	1 mg q 3-4 h
Oxymorphone Controlled-release	20 to 40 mg q 12 h	N/A	20 to 40 mg q 12 h	N/A
Combination opioid/NSAID preparations				
Codeine (with aspirin or acetaminophen)	180-200 mg q 3-4 h	130 mg q 3-4 h	60 mg q 3-4 h	60 mg q 2 h (IM/SC)
Hydrocodone (in Lorcet™)	30 mg q 3-4 h	N/A	10 mg q 3-4 h	N/A
Oxycodone (in Percocet™)	30 mg q 3-4 h	N/A	10 mg q 3-4 h	N/A
	Transdermal	-	Transdermal	-
Fentanyl (Duragsic Patch)	25 to 50 µg/hr	-	25 to 50 µg/hr	-

Adapted from Clinical Practice Guidelines for Cancer Pain Management, Agency for Health Care Policy and Research Guideline No. 9, AHCPR Publication No. 94-0592, March 1994, U.S. department of Health and Human Services and supplemented with information from: Guideline for the Management of Cancer Pain in Adults, American Pain Society, 2005, etc. **Codes & Footnotes:** N/A = not available. N/R = not recommended. IM = intramuscular. SC = subcutaneous.

[0088] The methods and compositions of the present invention are useful in preventing or treating all types of pain. Preferred types of pain to be treated by the present invention are neuropathic pain including diabetic neuropathy, acute herpes zoster (shingles), zoster associated pain, subacute zoster pain, postherpetic

neuralgia, trigeminal neuralgia, nerve injury, spinal cord injury pain, stump pain, phantom limb pain, radicular pain, HIV associated neuropathy, multiple sclerosis pain, poststroke pain, and temporomandibular joint disorder; cancer pain; chronic pain, including back pain, rheumatoid arthritis, osteoarthritis, myofascial pain, fibromyalgia, complex regional pain syndrome (CRPS) Type I and Type II, sympathetically mediated pain, Raynaud's disease and chronic pain syndrome; acute pain, including postsurgical pain, back pain, renal colic, tension and migraine headache, dysmenorrhea, joint pain, musculoskeletal pain, posttraumatic pain; pelvic pain; vulvodynia; burn pain; cystitis.

[0089] Chronic or intractable pain is often endured over many years or decades. Patients suffering from chronic pain often develop emotional problems which can lead to depression and in the worst case, attempted suicide. Long lasting pain often occurs particularly in peripheral nerves, skin, joints, in muscles, connective tissue, viscera, and in the back. In the United States alone, chronic pain causes a loss of more than 250 million working days per year.

[0090] A patient is usually considered to have chronic pain when complaints thereof last longer than three months. In the course of time, chronic pain can come completely to the fore and form an independent clinical syndrome. Today most of the clinical phenomena of chronic pain syndrome are explained as a permanent excitation of spinal convergence neurons. This excitation can be provoked by either visceral or somatic afferent stimulation.

[0091] Certain types of pain have complex etiologies. For example, neuropathic pain is generally a chronic condition attributable to injury or partial transection of a peripheral nerve, spinal cord or brain. This type of pain is characterized by hyperesthesia, or enhanced sensitivity to external noxious stimuli, allodynia, or application of an otherwise non-noxious stimuli, and paroxysmal pain. The hyperesthetic component of neuropathic pain does not respond to the same pharmaceutical interventions as does more generalized and acute forms of pain. Neuropathic pain is a form of chronic pain that can persist for months, years, or

decades following an injury and results from damage to peripheral nerves, nerve roots, the spinal cord, or certain brain regions. It differs from nociceptive pain in terms of duration, characteristics, underlying mechanisms and treatment (Jensen TS (pp. 799-814); Scadding, JW (pp. 815-834); Scadding JW (pp. 835-850); Boivie J (pp. 879-914) and Beric A (pp. 915-928), in *Textbook of Pain*, Wall, PD and Melzack, R, eds., Churchill Livingstone, London 4th edn,(1999)). Patients with neuropathic pain experience a combination of positive and negative sensory, motor, and autonomic signs and symptoms. Positive sensory symptoms include pain, paresthesia (abnormal sensation, either evoked or spontaneous), dysesthesia (evoked or spontaneous unpleasant, abnormal sensation), hyperalgesia (increased response to a normally painful stimulus), and allodynia (painful response to a nonnoxious stimulus). Negative sensory symptoms involve a loss of sensitivity to stimulation in general and painful stimuli in particular (hypoesthesia and hypoalgesia, respectively). ((Backonja M et al, *Pain Medicine*, 2004;5(S1):S28-S47). Neuropathic pain can accompany nociceptive pain, and multiple treatment strategies may be required for optimal alleviation of pain (Portenoy, R.K., in *Towards a New Pharmacology of Pain*, Basbaum, A.I. and Besson, J.M., eds., John Wiley & Sons Ltd, New York (1991), pp. 393 *et seq.*; Devor M, *et al.*, in *Towards a New Pharmacotherapy of Pain*, Basbaum, A.I. and Besson, J.M., eds., John Wiley & Sons, New York (1991), pp. 417 *et seq.*).

[0092] Other pain syndromes believed to have a neuropathic component are stump pain, fibromyalgia, cancer pain, myofascial pain, polyarteritis nodosa, osteomyelitis, burns involving nerve damage, AIDS related pain syndromes, and connective tissue disorders, such as systemic lupus erythematosus, systemic sclerosis, polymyositis, and dermatomyositis, and the like.

[0093] Acute pain is usually a consequence of an identifiable insult, such as surgery or other trauma, or a consequence of a disease, *e.g.*, kidney stones, mechanical low back pain, etc. It may be treated with parenteral and oral opioid analgesics, NSAIDs, and more recently, COX-2 selective NSAIDs. Recent

surveys have suggested that the management of acute post-surgical pain may be inadequate due in part to dose-related side effects of opioids (e.g., nausea, vomiting, sedation, constipation and rare but potentially fatal respiratory arrest, shock, and cardiac arrest) and NSAIDs (e.g., gastrointestinal bleeding). Acute pain may be recurrent, as in acute low back pain, migraine, cluster headaches and tension headaches.

[0094] All modes of co-administration are contemplated. Administration of the μ -opioid receptor agonist and levorphanol, a putative κ_3 -opioid receptor agonist may be via oral, subcutaneous, direct intravenous, slow intravenous infusion, continuous intravenous infusion, intravenous or epidural patient controlled analgesia (PCA and PCEA), intramuscular, intrathecal, epidural, intracisternal, intramuscular, intraperitoneal, transdermal, topical, transmucosal, buccal, sublingual, transmucosal, inhalation, intranasal, epidural, intra-auricular, intranasal, rectal or ocular routes for systemic or local analgesic effects. The formulations can, where appropriate, be conveniently presented in discrete dosage units and can be prepared by any of the methods well known in the art of pharmacy.

[0095] All pharmaceutical dosage forms are contemplated. Administration of the μ -opioid receptor agonist and levorphanol, a putative κ_3 -opioid receptor agonist may be in the form of oral solutions and suspensions, tablets, capsules, lozenges, effervescent tablets, transmucosal films, suppositories, buccal products, oral muco-retentive products, topical creams, ointments, gels, films and patches, transdermal patches, abuse deterrent and abuse resistant formulations, sterile solutions, suspensions and depots for parenteral use, and the like, administered as immediate release, sustained release, delayed release, controlled release, extended release and the like.

[0096] The μ -opioid receptor agonist and levorphanol may be administered as a single pharmaceutical composition. That is, the μ -opioid receptor agonist and levorphanol may be formulated together so that both active agents are contained

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in one pharmaceutical composition. For example, the μ -opioid receptor agonist and levorphanol may be formulated together in a unit dosage form. Suitable unit dosage forms include tablets, pills, capsules, caplets, hard gelatin capsule in powder or granular form, trochet, soft gelatin capsule, orally disintegrating tablets, transmucosal film, lozenge, buccal dosage form, nasal solutions and suspensions, parenteral, immediate release, controlled release, topical ointment, cream or patch, transdermal patch, depot, dry powder inhaler, aerosolized inhaler, liposomal and the like. In one embodiment, the μ -opioid receptor agonist and levorphanol are given with suitable pharmaceutical carriers as an immediate release capsule. In another embodiment, μ -opioid receptor agonist and levorphanol are given as a controlled release tablet every 12 or twenty four hours.

[0097] Levorphanol and the μ -opioid receptor agonist need not be administered together, although there must be a reasonable temporal relationship between the administration of levorphanol and μ -opioid receptor agonist, in other words, the μ -opioid receptor agonist is usually present in detectable plasma concentrations at the time of administration or coadministration of levorphanol. In one embodiment, a subject receiving oral immediate release morphine every four hours may receive oral levorphanol 2 or 3 hours after the last dose of morphine. In another embodiment, a subject receiving controlled release oxycodone every 12 hours may receive oral levorphanol 6, 8 or 10 hours after the last dose of oxycodone. In another embodiment, a subject receiving transdermal fentanyl every three days may receive sublingual levorphanol 1, 2 or 3 days after the last dose of transdermal fentanyl. In another embodiment, a patient receiving epidural controlled release morphine may receive injectable levorphanol 3, 9, or 18 hours after the morphine epidural injection. In another embodiment, a subject receiving weekly transdermal sufentanil may receive oral levorphanol 6, 12, 18 or 140 hours after the last dose of transdermal sufentanil. In another embodiment, a subject receiving transdermal alfentanil every week may receive oral levorphanol

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every 6 to 8 hours daily while receiving alfentanil. In another embodiment, a subject receiving controlled release morphine every 24 hours may receive oral levorphanol 2, 6, 8, 10, 18 or 22 hours after the last dose of morphine as a rescue analgesic for the treatment of breakthrough pain.

[0098] In certain cases it may be desirable to administer levorphanol and the μ -opioid receptor agonist separately. For example, the half life or duration of action of levorphanol is longer than that of the μ -opioid receptor agonists hydromorphone, oxycodone or morphine. This may make administration as a single pharmaceutical composition impractical under some circumstances. In other instances, the dose of the μ -opioid receptor agonist may need to be adjusted without a need to adjust the dose of levorphanol, thereby making separate administration more attractive. In yet other instances, subjects receiving regular doses of a μ -opioid receptor agonist such as fentanyl or hydromorphone may have transitory or episodic pain which requires intermittent coadministration of small doses of levorphanol as a rescue analgesic to treat the breakthrough pain. Since breakthrough pain can be from incident pain, end of dose failure, other causes or idiopathic and often occur unpredictably, the levorphanol dose may be administered at intervals that can range from infrequent (e.g., every 1 or two days) to frequent (e.g., every few hours).

[0099] Of course it will be readily appreciated by individuals familiar with the art that the rescue analgesic dosage for the treatment of breakthrough pain may vary. Some patients cannot tolerate large doses of rescue analgesics and may receive lower doses, administered more frequently, even if this means recurring episodes of breakthrough pain. Typically, the rescue analgesic medication dose is calculated based on the dose of the baseline, scheduled, around the clock or intermittently administered "baseline medication". When calculated in morphine analgesic equivalents, the dose of each rescue used to treat the breakthrough pain will range from 2% to 15% of the daily dose of the baseline, scheduled, around the clock or intermittently administered "baseline

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medication". Typically, each rescue analgesic is 5 to 15% of the daily dose of the baseline medication, preferably 5 to 10% the daily dose of the baseline medication. For example, if the baseline medication is a once-a-day oral controlled release morphine given at a daily dose of 200 mg, the rescue analgesic dose is typically is between about 10 mg to about 30 mg of oral morphine, or optionally, with another drug whose dose may be calculated, using the morphine analgesic equivalence. If there is an increase in the dose of the baseline medication (e.g., with disease progression), it is well known in the art that the dose of the rescue analgesic should also be increased. If the dose of baseline oral morphine increased from 200 mg per day to 400 mg per day, the dose of the oral morphine rescue analgesic would be increased from between about 10 to about 30 mg (old typical dose range) to between about 20 to about 60 mg per dose (new typical dose range). The dose of rescue analgesic opioid as a percentage of daily dose of baseline medication remains unchanged.

[00100] Rescue analgesics are typically the immediate release versions of extended release drugs. Use of the same drug for the treatment of baseline pain and breakthrough pain has been encouraged for several reasons, including the ease of causality assessment for side effects, transparent determination of the adequacy of current rescue doses and easy calculation of rescue dose increases, when the baseline medication dose is increased (without the complexity of calculating new doses through the use of analgesic equivalence and analgesic conversion tables). An exception to the use of the same opioid for the treatment of ongoing or baseline pain and breakthrough pain has been the use of fentanyl, a short acting μ -opioid agonist, in the form of a transmucosal lollipop (Actiq™), approved by the FDA in November, 1998. There is no prior art on the use of levorphanol or κ_3 -opioid receptor agonist as rescue analgesics for the treatment of breakthrough pain in patients receiving μ -opioid agonists. In fact, rescue analgesics are typically drugs with a short half life, to allow for rapid onset and offset of supplemental effect and long half life drugs such as levorphanol (half-

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life approximately 11 hours) acting analgesics are discouraged for the treatment of breakthrough pain. Surprisingly, the administration of levorphanol as a rescue analgesic for the treatment of breakthrough pain in patients receiving baseline scheduled, around the clock or intermittently administered μ -opioid agonists can provide robust analgesia with fewer side effects.

[00101] The term “ μ -opioid receptor agonist”, “ μ -opioid”, “ μ -opioid agonist” or “ μ -agonist” as used herein all refer to a substance which activates a μ -opioid receptor. The μ -opioid receptors mediate the actions of morphine and morphine-like opioids. Highly selective agonists for the μ -opioid receptors include [D-Ala²,MePhe⁴,Gly(ol)⁵] enkephalin (DAMGO), etorphine, fentanyl, sufentanil and bremazocine. Antagonists for the μ -opioid receptor include naloxone, naltrexone, D-Phe-Cys-Trp-D-Trp-Orn-Thr-PenThr-NH₂ (CTOP), diprenorphine, (3-funaltrexamine, naloxonazine, nalorphine, nalbuphine, and naloxone benzoylhydrazone.

[00102] The μ -opioid receptor agonist may be selected from the group including alfentanil, alphaprodine, anileridine, buprenorphine, butorphanol, carfentanil, codeine, dezocine, dextromoramide, diamorphine, dihydrocodeine, dihydrocodeinone, dihydromorphine, fentanyl, hydrocodone, hydromorphone, levomethadone, lofentanil, meperidine, meptazinol, methadone, morphine, nalbuphine, normethadone, normorphine, oxycodone, oxymorphone, pentazocine, phenazocine, propiram, propoxyphene, remifentanil, sufentanil and tramadol and their pharmaceutically acceptable salts, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates, as a racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof. Preferably, the μ -opioid agonist is oxycodone, oxymorphone, codeine, morphine, methadone, hydromorphone, hydrocodone, dihydrocodeine, tapentadol, fentanyl, sufentanil, alfentanil, lofentanil, carfentanil and remifentanil. For the purposes of the present invention, oxycodone is classified

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as a μ -opioid agonist. It is recognized that oxycodone may exert some of its antinociceptive and analgesic effects at other opioid receptors such as κ_1 and κ_2 .

[00103] For the purposes of this invention and without being bound by theory, the term " κ_3 -opioid receptor agonist" as used herein refers to selective κ_3 -opioid receptor agonists wherein the antinociceptive effects thereof are substantially enhanced by naloxone benzoylhydrazone (NalBzoH). Antagonists which selectively block μ , δ , κ_1 and κ_2 , analgesia have little effect on κ_3 analgesia. Antagonists of the κ_3 -opioid receptors include naloxone, naltrexone and diprenorphine. Preferably, the κ_3 -opioid receptors agonist is levorphanol, a putative κ_3 -opioid receptors agonist. The present invention does not require that the synergistic effects of levorphanol with μ -opioid agonist be a consequence of activation of the κ_3 -opioid receptor.

[00104] The term "pharmaceutically acceptable salt" as used herein refers to a salt which is toxicologically safe for human and animal administration. Nonlimiting examples of salts include hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates, bitartrates, phosphates, malates, maleates, napsylates, fumarates, succinates, acetates, terephthalates, pamoates and pectinates. Preferably, the pharmaceutically acceptable salt of levorphanol is a tartrate. Preferably, the pharmaceutically acceptable salt of morphine is a hydrochloride, a sulfate or a tartrate.

[00105] The subanalgesic and analgesic dosages and dosage ranges of the μ -opioid agonist and levorphanol in the present invention are expressed as mg of base or mg of pharmaceutically acceptable salt. For example, a dose of about 5 mg of a μ -opioid receptor agonist given orally, expressed in morphine analgesic equivalents, can be considered 5 mg of oral morphine base, or 5 mg of morphine sulfate. Similarly, a dose of 5 mg of oral levorphanol can be considered 5 mg of levorphanol base or 5 mg of levorphanol tartrate.

[00106] The term "subanalgesic dosage" as used herein refers to a dosage of a μ -opioid agonist given alone or levorphanol, given alone which dosage does not

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result in the production of meaningful analgesia when administered to a human or antinociception when administered to non-human subjects requiring alleviation of pain. To this extent, it is well known that the lower threshold for an initial dosage of morphine, a μ -opioid receptor agonist, which results in production of analgesia in a naive human adult is 30 mg every three to four hours when administered by the oral route and 10 mg every three to four hours administrable by the intravenous route. Similarly, the lower threshold for an initial dosage of levorphanol resulting in production of analgesia in a naive human adult is 4 mg every 6 to 8 hours, when administered by the oral route and 2 mg every 6 to 8 hours when administered intravenously. (Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, 1994). Accordingly, the term "subanalgesic dosage" includes within its scope dosages falling below such lower thresholds. This term will also cover direct administration of the μ -agonist or levorphanol as well as administration which includes controlled-release, sustained release, modified release or extended release of the μ -agonist or levorphanol as described herein after. Of course it will be appreciated that a subanalgesic dosage of a μ -agonist or levorphanol in accordance with the invention will be dependent upon the mode or route of administration thereof.

[00107] Subanalgesic doses of other μ -opioid receptor agonists are well known in the art. They can also be readily determined from the specified morphine doses by a given route, using equianalgesic conversion Tables referenced herein and by using the test methods described herein.

[00108] Suitable subanalgesic dosages of such opioid agonists may be readily determined by those of skill in the art. For example, in the case wherein the μ -opioid agonist comprises morphine or analog or derivative or pharmaceutically acceptable salts thereof, an initial subanalgesic dosage of such agonist for a human adult through an intracerebroventricular or spinal route may be between about 0.01 mg and about 0.25 mg per day, or in the case of another μ -

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opioid receptor agonist give by the same route of administration, this can be expressed as about 0.01 mg and about 0.25 mg per day, expressed in morphine analgesic equivalents. The analgesic equivalence of two μ -opioid receptor agonists can easily be calculated by as described elsewhere. It will be appreciated that this dosage of the μ -opioid receptor agonist may be administered in immediate release or controlled-release forms. For example, controlled-release dosage forms as described hereinafter may be administered every 12 or 24 hours comprising respectively about 3 or 6 times the four hourly dosage given above. In this regard, it is well known that the change from immediate release dosages to controlled release dosages of an opioid is a milligram to milligram conversion which results in the same total 'around-the-clock' dose of the opioid (Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, 1994).

[00109] An initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route, expressed in morphine analgesic equivalents, may be between about 0.5 mg and about 7.5 mg, preferably between about 0.5 mg and about 3.0 mg, more preferably between about 0.5 mg and about 2.5 mg, and most preferably between about 0.5 mg and about 2.0 mg every four hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage may be between about 1.5 mg and about 10.5 mg, preferably between about 1.5 mg and about 9.0 mg, more preferably between about 1.5 mg and about 7.5 mg and most preferably between about 1.5 mg and about 6.0 mg every 12 hours, or between about 3.0 mg and about 21.0 mg, preferably between about 3.0 mg and about 18.0 mg, more preferably between about 3.0 mg and about 15 mg and most preferably between about 3.0 mg and about 12.0 mg every 24 hours.

- [00110] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route, expressed in morphine analgesic equivalents, is between about 2.0 mg and about 25.0 mg, preferably between about 5.0 mg and about 20.0 mg, more preferably between about 5.0 and about 15 mg every four hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage may be between about 6.0 mg and about 75.0 mg, preferably between about 15.0 mg and about 60.0 mg, more preferably between about 15.0 mg and about 45.0 mg every 12 hours, or between about 12.0 mg and about 150.0 mg, preferably between about 30.0 mg and about 120.0 mg, more preferably between about 30.0 mg and about 90.0 mg every 24 hours.
- [00111] An initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human child through an intracerebroventricular or spinal route, expressed in morphine analgesic equivalents, may be between about 0.01 mg and about 0.25 mg per day.
- [00112] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salts thereof for a naive human child through a subcutaneous route, expressed in morphine analgesic equivalents, is between about 0.01 mg/kg and about 0.09 mg/kg every four hours.
- [00113] An initial subanalgesic dosage of μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human child through an intravenous route, expressed in morphine analgesic equivalents, may be between about 0.01 mg/kg and about 0.04 mg/kg every four hours.
- [00114] Alternatively, an initial subanalgesic dosage of μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route, expressed in morphine analgesic equivalents, may be between about 0.1 mg/kg and about 0.4 mg/kg every four hours.

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- [00115] Suitably, an initial subanalgesic dosage of μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive lower animal through an oral or parenteral route, expressed in morphine analgesic equivalents, is between about 0.5 mg/kg and about 5 mg/kg every three to six hours.
- [00116] Suitably, an initial subanalgesic dosage of the μ -opioid agonist or pharmaceutically acceptable salt thereof, for a naive human adult through intravenous patient controlled analgesia, expressed in morphine analgesic equivalents, is between about 0.1 mg and about 0.75 mg every 3 to 10 minutes as required, preferably between about 0.1 mg and about 0.5 mg every 3 to 10 minutes and more preferably between about 0.1 mg and about 0.35 mg every 3 to 10 minutes as required.
- [00117] The duration of analgesic effect (or dosing frequency) of a μ -opioid receptor agonist will vary depending on the route of administration and the nature of the dosage form (immediate release, controlled release, etc). Consequently, the dosage of μ -opioid receptor agonist can conveniently be expressed in terms of "mg for each hour of its intended duration of effect". This permits for the dosage specification to be adjusted to accommodate difference the duration of effect. For example a μ -opioid receptor agonist whose dose by the oral route of administration is specified as "5 mg for each hour of its intended duration of effect", "expressed in morphine analgesic equivalents" when given orally as a 12 hour controlled release formulation will have a dose of 60 mg every 12 hours by mouth (5 mg x 12 hour dosing frequency or intended duration of effect = 60 mg every 12 hour). For another oral μ -opioid agonist, whose relative analgesic potency to oral morphine is 2:1 when given *orally* (i.e., it is twice as potent orally as oral morphine or it provides analgesia comparable by the oral route to oral morphine with about half the mg dose required by morphine) and whose relative analgesic potency to oral morphine is 4:1 when given intravenously (i.e., it is four times as potent intravenously as oral morphine or it provides analgesia comparable by the intravenous route to oral morphine with about one quarter the

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mg dose required by morphine), the oral and intravenous doses (equivalent to oral morphine 5 mg for each hour of its intended duration of effect, expressed in morphine analgesic equivalents”), would be 2.5 mg per hour, in the case of the μ -opioid agonist given orally and 1.25 mg per hour, in the case of the μ -opioid agonist given intravenously. If this drug is administered as a once-a-day controlled release oral formulation, the dose would be about 60 mg per day by mouth.

[00118] Using this approach, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.125 mg and about 1.875 mg; preferably between about 0.125 mg and about 1.25 mg and more preferably between about 0.125 mg and about 0.875 mg.

[00119] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through a oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.5 mg and about 6.25 mg or between about 0.5 mg and about 5 mg; preferably between about 0.5 mg and about 3.75 mg or between about 0.5 mg and about 2.5 mg; and more preferably between about 0.5 mg and about 1.875 mg.

[00120] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through an epidural route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.01 mg and about 0.5 mg; between about 0.01 mg and about 0.25 mg or between about 0.01 mg and about 0.125 mg.

[00121] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human adult through a

spinal (intrathecal) route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.001 mg and about 0.004 mg; or about 0.001 mg and about 0.002 mg.

[00122] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.025 mg/kg and about 0.1mg/kg or between about 0.025 mg/kg and about 0.1mg/kg or between about 0.025 mg/kg and about 0.05mg/kg.

[00123] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.0025 mg/kg and about 0.01 mg/kg.

[00124] Suitably, an initial subanalgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a naive lower animal through an oral or parenteral route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.01 mg/kg and about 1.25 mg/kg.

[00125] In the case of levorphanol or a pharmaceutically acceptable salt thereof, a suitable initial subanalgesic dosage for a human adult through an intracerebroventricular or spinal route may be between about 0.01 mg and about 0.1 mg per day.

[00126] An initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a naive human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route may be between about 0.2 mg and about 2.0 mg, preferably between about 0.5 mg and about 2.0 mg, more preferably between about 1.0 and about 2.0 mg every six to eight hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage

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may be between about 0.4 mg and about 4.0 mg, preferably between about 1.0 mg and about 4.0 mg, more preferably between about 2.0 mg and about 4.0 mg every 12 hours, or between about 0.8 mg and about 8.0 mg, preferably between about 2.0 mg and about 8.0 mg, more preferably between about 4.0 mg and about 8.0 mg every 24 hours.

[00127] Suitably, an initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route is between about 0.15 mg and about 4.0 mg, preferably between about 0.5 mg and about 4.0 mg, more preferably between about 2.0 and about 4.0 mg every six to eight hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage may be between about 0.3 mg and about 8.0 mg, preferably between about 1.0 mg and about 8.0 mg, more preferably between about 4.0 mg and about 8.0 mg every 12 hours, or between about 0.6 mg and about 16.0 mg, preferably between about 2.0 mg and about 16.0 mg, more preferably between about 8.0 mg and about 16.0 mg every 24 hours.

[00128] An initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human child through an intracerebroventricular spinal route may be between about 0.01 mg and about 0.1 mg per day.

[00129] Suitably, an initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a naïve human child through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route is between about 0.002 mg/kg and about 0.03 mg/kg, preferably between about 0.005 mg/kg and about 0.03 mg/kg, more preferably between about 0.01 mg/kg and about 0.03 mg/kg every six to eight hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage may be between about 0.004 mg/kg and about 0.06 mg/kg, preferably between about 0.01 mg and about 0.06 mg, more preferably between about 0.02 mg/kg and about 0.06 mg/kg every 12 hours, or between about 0.008 mg/kg and about 0.12 mg/kg, preferably between about 0.02

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mg/kg and about 0.12 mg/kg, more preferably between about 0.04 mg/kg and about 0.12 mg every 24 hours.

[00130] Suitably, an initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route is between about 0.002 mg/kg and about 0.06 mg/kg, preferably between about 0.007 mg/kg and about 0.06 mg/kg, more preferably between about 0.03 mg/kg and about 0.06 mg/kg every six to eight hours. Alternatively, in controlled-release dosage form, the initial subanalgesic dosage may be between about 0.004 mg/kg and about 0.12 mg/kg, preferably between about 0.014 mg/kg and about 0.12 mg/kg, more preferably between about 0.06 mg/kg and about 0.12 mg every 12 hours, or between about 0.008 mg/kg and about 0.24 mg/kg, preferably between about 0.028 mg/kg and about 0.24 mg/kg, more preferably between about 0.12 mg/kg and about 0.24 mg every 24 hours.

[00131] Suitably, an initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof, for a naive human adult through intravenous patient controlled analgesia is between about 0.05 mg and about 0.25 mg every 3 to 20 minutes as required; preferably between about 0.05 mg and about 0.15 mg every 3 to 20 minutes as required; more preferably between about 0.05 mg and about 0.1 mg every 3 to 20 minutes as required.

[00132] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive lower animal through an oral or parenteral route is between about 0.2 mg/kg and about 3 mg/kg every six to eight hours.

[00133] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect, is between about 0.025 mg and about 0.333 mg

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or between about 0.025 mg and about 0.166 mg; or between about 0.025 mg and about 0.0833 mg.

[00134] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, is between about 0.01875 mg and about 0.666 mg or between about 0.01875 mg and about 0.5 mg; preferably between about 0.01875 mg and about 0.333 mg; and more preferably between about 0.01875 mg and about 0.166 mg.

[00135] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult through an epidural route for each hour of its intended duration of effect is between about 0.002 mg and about 0.1 mg; or between about 0.002 mg and about 0.075 mg; or between about 0.002 mg and about 0.05 mg.

[00136] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult through a spinal (intrathecal) route for each hour of its intended duration of effect is between about 0.00005 mg and about 0.001 mg; or between about 0.00005 mg and about 0.0005 mg; or between about 0.00005 mg and about 0.00025 mg.

[00137] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.00025 mg/kg and about 0.01 mg/kg; or between about 0.00025 mg/kg and about 0.005 mg/kg.

[00138] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a naive human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each

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hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.000125 mg/kg and about 0.005 mg/kg.

[00139] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a naive lower animal through an oral or parenteral route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents is between about 0.025 mg/kg and about 0.5 mg/kg;

[00140] Of course it will be readily appreciated by individuals familiar with the art that the subanalgesic dosage of μ -opioid receptor agonist or levorphanol and their pharmaceutically acceptable salts will vary considerably from patient to patient, based on patient related factors (e.g., receptor up or down regulation, receptor density, pharmacokinetics, pharmacodynamics, coping skills, psychological health, etc) and pain related factors (e.g., pain intensity, etiology, location). Further, it will be readily appreciated by individuals familiar with the art that the initial subanalgesic dosage of μ -opioid receptor agonist or levorphanol agonist may increase with disease progression (in an opioid non-naïve or opioid tolerant patient) from the initial subanalgesic dose (in an opioid naïve subject). This is consistent with the use of opioid analgesics, where the initial dose is usually low and if required, increased as needed to achieve a balance between analgesia and side effects.

[00141] The term "enhancing the analgesic effect" of the μ -opioid receptor agonist as used herein refers to increasing the speed of onset, peak, duration and overall magnitude of analgesic effect.

[00142] The term "analgesic dosage" as used herein refers to a dosage of a μ -opioid agonist given alone or levorphanol, given alone which dosage results in the production of meaningful analgesia when administered to a human or antinociception when administered to non-human subjects requiring alleviation of pain.

- [00143] This term will also cover direct administration of the μ -agonist or levorphanol as well as administration which includes controlled-release, sustained release, modified release or extended release of the μ -agonist or levorphanol as described herein after. Of course it will be appreciated that analgesic dosage of a μ -agonist or levorphanol in accordance with the invention will be dependent upon the mode or route of administration thereof.
- [00144] Analgesic doses of other μ -opioid receptor agonists are well known in the art. They can also be readily determined from the specified morphine doses by a given route, using equianalgesic conversion Tables referenced herein and by using the test methods described herein.
- [00145] Suitable analgesic dosages of such opioid agonists may be readily determined by those of skill in the art. For example, in the case wherein the μ -opioid agonist comprises morphine or a pharmaceutically acceptable salt thereof, an analgesic dosage of such agonist for a human adult through an intracerebroventricular or spinal route may be between about 0.25 mg and about 5 mg per day. It will be appreciated that this dosage may be administered in immediate release or controlled-release forms. For example, controlled-release dosage forms as described hereinafter may be administered every 12 or 24 hours comprising, respectively, about 3 or 6 times the four hourly dosage given above. In this regard, it is well known that the change from immediate release dosages to controlled release dosages of an opioid is a milligram to milligram conversion which results in the same total 'around-the-clock' dose of the opioid (Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, 1994).
- [00146] An analgesic dosage of μ -opioid agonist or a pharmaceutically acceptable salt thereof for a human adult through a subcutaneous, intravenous, intramuscular or inhaled route, expressed in morphine analgesic equivalents, may be between about 7.5 mg and about 60 mg every four hours. Alternatively,

in controlled-release dosage form, the analgesic dosage, expressed in morphine analgesic equivalents, may be between about 10.5 mg and about 180 mg every 12 hours, or between about 21 and about 360 mg every 24 hours.

[00147] Suitably, an analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for through an oral, rectal, buccal, transmucosal or sublingual route, expressed in morphine analgesic equivalents, is between about 25 and about 120 mg every four hours. Alternatively, in controlled-release dosage form, the analgesic dosage, expressed in morphine analgesic equivalents, may be between about 75 mg and about 360 mg every 12 hours, or between about 150 mg and about 720 mg every 24 hours.

[00148] An analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for a human child through an intracerebroventricular or spinal route, expressed in morphine analgesic equivalents, may be between about 0.25 mg and about 3 mg per day.

[00149] Suitably, an analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for a human child through a subcutaneous route, expressed in morphine analgesic equivalents, is between about 0.09 mg/kg and about 1 mg/kg every four hours.

[00150] An analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for a human child through an intravenous route, expressed in morphine analgesic equivalents, may be between about 0.04 mg/kg and about 1 mg/kg every four hours.

[00151] Alternatively, an analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route, expressed in morphine analgesic equivalents, may be between about 0.4 mg/kg and about 3 mg/kg every four hours.

[00152] Suitably, an analgesic dose of a μ -opioid agonist or pharmaceutically acceptable salts thereof for a human adult through intravenous patient controlled analgesia, expressed in morphine analgesic equivalents, is between about 0.75 mg

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and about 6 mg every 3 to 10 minutes; between about 0.5 mg and about 6 mg every 3 to 10 minutes or between about 0.35 mg and about 6 mg every 3 to 10 minutes.

[00153] Suitably, an analgesic dosage of μ -opioid agonist or pharmaceutically acceptable salts thereof for a naive lower animal through an oral or parenteral route, expressed in morphine analgesic equivalents, is between about 5 mg/kg and about 25 mg/kg every three to six hours.

[00154] Doses can also be expressed in morphine analgesic equivalents for each hour of its intended duration. An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 1.875 mg and about 15 mg; or between about 0.125 mg and about 15 mg; or between about 0.875 mg and about 15 mg.

[00155] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human adult through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 6.25 mg and about 30 mg; between about 5 mg and about 30 mg; between about 3.75 mg and about 30 mg; between about 2.5 mg and about 30 mg; or between about 1.875 mg and about 30 mg.

[00156] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human adult through an epidural route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.5 mg and about 5 mg; between about 0.25 mg and about 5 mg; or between about 0.125 mg and about 5 mg.

[00157] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human adult through a spinal (intrathecal) route for each hour of its intended duration of effect, expressed in

morphine analgesic equivalents, is between about 0.004 mg and about 0.5 mg; or between about 0.002 mg and about 0.5 mg; or between about 0.001 mg and about 0.5 mg.

[00158] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human child through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.1 mg/kg and about 1 mg/kg; or between about 0.05 mg/kg and about 1 mg/kg.

[00159] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a human child through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.01 mg/kg and about 0.5 mg/kg.

[00160] An initial analgesic dosage of a μ -opioid receptor agonist or pharmaceutically acceptable salt thereof for a lower animal through an oral or parenteral route for each hour of its intended duration of effect, expressed in morphine analgesic equivalents, is between about 0.01 mg/kg and about 1.25 mg/kg.

[00161] In the case of levorphanol or pharmaceutically acceptable salt thereof, a suitable analgesic dosage for a human adult through an intracerebroventricular or spinal route, may be between about 0.1 mg and about 5 mg per day.

[00162] An analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route, may be between about 2 mg and about 12 mg, every six to eight hours. Alternatively, in controlled-release dosage form, the analgesic dosage, may be between about 4 mg and about 50 mg, every 12 hours, or between about 8 mg and about 100 mg, every 24 hours.

[00163] Suitably, an analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human adult through an oral, rectal, buccal,

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transmucosal or sublingual route is between about 4 mg and about 36 mg, every six to eight hours. Alternatively, in controlled-release dosage form, the analgesic dosage may be between about 8 mg and about 36 mg, every 12 hours, or between about 16 mg and about 144 mg, every 24 hours.

[00164] An analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human child through an intracerebroventricular spinal route may be between about 0.1 mg and about 2 mg per day.

[00165] Suitably, an analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human child through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route is between about 0.03 mg/kg and about 1 mg/kg, every six to eight hours. Alternatively, in controlled-release dosage form, the analgesic dosage may be between about 0.06 mg/kg and about 1.2 mg/kg, every 12 hours, or between about 0.12 mg/kg and about 2.4 mg/kg, every 24 hours.

[00166] Suitably, an analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a human child through an oral, rectal, buccal, transmucosal or sublingual route is between about 0.06 mg/kg and about 1.2 mg/kg, every six to eight hours. Alternatively, in controlled-release dosage form, the analgesic dosage may be between about 0.12 mg/kg and about 2.4 mg/kg, every 12 hours, or between about 0.24 mg/kg and about 5 mg/kg, every 24 hours.

[00167] Suitably, an analgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof for a lower animal through an oral or parenteral route is between about 3 mg/kg and about 15 mg/kg every six to eight hours.

[00168] Suitably, an analgesic dose of levorphanol or a pharmaceutically acceptable salt thereof for a human adult through intravenous patient controlled analgesia, is between about 0.25 mg and about 3 mg every 3 to 20 minutes; or between about 0.15 mg and about 3 mg every 3 to 20 minutes; or between about 0.01 mg and about 3 mg every 3 to 20 minutes.

- [00169] Doses of levorphanol can also be expressed for each hour of its intended duration. An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route for each hour of its intended duration of effect is between about 0.333 mg and about 2 mg; between about 0.166 mg and about 2 mg; or between about 0.0833 mg and about 2 mg.
- [00170] An initial analgesic dosage of levorphanol agonist or pharmaceutically acceptable salt thereof for a human adult through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, is between about 0.666 mg and about 6 mg; between about 0.5 mg and about 6 mg; between about 0.333 mg and about 6 mg; or between about 0.166 mg and about 6 mg.
- [00171] An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a human adult through an epidural route for each hour of its intended duration of effect, is between about 0.1 mg and about 2 mg; between about 0.075 mg and about 2 mg; or between about 0.05 mg and about 2 mg.
- [00172] An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a human adult through a spinal (intrathecal) route for each hour of its intended duration of effect, is between about 0.001 mg and about 0.1 mg; between about 0.0005 mg and about 0.1 mg; or between about 0.00025 mg and about 0.1 mg.
- [00173] An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a human child through an oral, rectal, buccal, transmucosal or sublingual route for each hour of its intended duration of effect, is between about 0.01 mg/kg and about 0.2 mg/kg; or between about 0.005 mg/kg and about 0.2 mg/kg.
- [00174] An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a human child through a subcutaneous, intravenous,

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intramuscular, intranasal or inhaled route for each hour of its intended duration of effect is between about 0.005 mg/kg and about 0.1 mg/kg.

[00175] An initial analgesic dosage of levorphanol or pharmaceutically acceptable salt thereof for a lower animal through an oral or parenteral route for each hour of its intended duration of effect, is between about 0.5 mg/kg and about 5 mg/kg.

[00176] Of course it will be readily appreciated by individuals familiar with the art that the analgesic dosage of μ -opioid receptor agonist or levorphanol will vary considerably from subject to subject, based on subject related factors (e.g., receptor up or down regulation, receptor density, pharmacokinetics, pharmacodynamics, coping skills, psychological health, etc) and pain related factors (e.g., pain intensity, etiology, location). Further, it will be readily appreciated by individuals familiar with the art that the initial analgesic dosage of μ -opioid receptor agonist or levorphanol agonist may increase with disease progression. This is consistent with the use of opioid analgesics, where the initial dose is usually low and if required, increased as needed to achieve a balance between analgesia and side effects.

[00177] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult for the treatment of breakthrough pain as required through an oral, rectal, buccal, transmucosal or sublingual route is between about 0.25 mg and about 4 mg; between about 0.25 mg and about 3 mg or between about 0.25 mg and about 2 mg; between about 0.25 mg and about 1 mg or between about 0.25 mg and about 0.5 mg.

[00178] Suitably, an initial subanalgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a naive human adult for the treatment of breakthrough pain as required through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route is between about 0.125 mg and about 2 mg; between about 0.125 mg and about 1.5 mg; between about 0.125 mg and

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about 1 mg; between about 0.125 mg and about 0.5 mg; or between about 0.125 mg and about 0.25 mg.

[00179] Suitably, an initial analgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a human adult for the treatment of breakthrough pain as required through an oral, rectal, buccal, transmucosal or sublingual route is between about 4 mg and about 36 mg; between about 3 mg and about 36 mg, between about 2 mg and about 36 mg, between about 1 mg and about 36 mg and between about 0.5 mg and about 36 mg.

[00180] Suitably, an initial analgesic dosage of levorphanol or pharmaceutically acceptable salts thereof for a human adult for the treatment of breakthrough pain as required through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route is between about 2 mg and about 18 mg; between about 1.5 mg and about 18 mg, between about 1 mg and about 18 mg, between about 0.5 mg and about 36 mg and between about 0.25 mg and about 18 mg.

[00181] According to another aspect of the invention there is provided a method for producing analgesia to subjects which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising a subanalgesic dosage of a μ -opioid receptor agonist, its pharmaceutically acceptable salt, derivative, analog, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof and a subanalgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist its pharmaceutically acceptable salt, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof.

[00182] According to another aspect of the invention there is provided a method for producing analgesia to subjects which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid

receptor agonist, its pharmaceutically acceptable salt, derivative, analog, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof and a subanalgesic or analgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist its pharmaceutically acceptable salt, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof.

[00183] According to another aspect of the invention there is provided a method for producing analgesia to subjects which comprises administering to a human with breakthrough pain while receiving treatment with a μ -opioid receptor, levorphanol, a putative κ_3 -opioid receptor agonist its pharmaceutically acceptable salt, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof.

[00184] According to another aspect of the invention there is provided a method for producing analgesia to subjects which comprises administering to a human adult through intravenous patient controlled analgesia an analgesic dosage of a μ -opioid receptor agonist, its pharmaceutically acceptable salt, derivative, analog, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof and a subanalgesic or analgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist its pharmaceutically acceptable salt, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof.

[00185] According to another aspect of the invention there is provided a method for producing analgesia to subjects which comprises administering to a human adult through intravenous patient controlled analgesia an subanalgesic dosage of a μ -opioid receptor agonist, its pharmaceutically acceptable salt, derivative, analog, ester, solvate, complex, polymorph, hydrate, as a racemate or an

individual diastereoisomer or enantiomeric isomer thereof or mixture thereof and a subanalgesic dosage of levorphanol, a putative κ_3 -opioid receptor agonist its pharmaceutically acceptable salt, ester, solvate, complex, polymorph, hydrate, as a racemate or an individual diastereoisomer or enantiomeric isomer thereof or mixture thereof.

[00186] In one method of the invention, the subanalgesic dose of μ -opioid agonist or pharmaceutically acceptable salts thereof for a for a naive human adult through intravenous patient controlled analgesia, expressed in morphine analgesic equivalents, is between about 0.1 mg and about 0.75 mg every 3 to 10 minutes as required, preferably between about 0.1 mg and about 0.5 mg every 3 to 10 minutes and more preferably between about 0.1 mg and about 0.35 mg every 3 to 10 minutes as required.

[00187] In another method of the invention, an initial subanalgesic dosage of levorphanol or a pharmaceutically acceptable salt thereof, for a naive human adult through intravenous patient controlled analgesia is between about 0.05 mg and about 0.25 mg every 3 to 20 minutes as required; preferably between about 0.05 mg and about 0.15 mg every 3 to 20 minutes as required; more preferably between about 0.05 mg and about 0.1 mg every 3 to 20 minutes as required.

[00188] In one method of the invention, the analgesic dose of a μ -opioid agonist or pharmaceutically acceptable salts thereof for a human adult through intravenous patient controlled analgesia, expressed in morphine analgesic equivalents, is between about 0.75 mg and about 6 mg every 3 to 10 minutes; between about 0.5 mg and about 6 mg every 3 to 10 minutes or between about 0.35 mg and about 6 mg every 3 to 10 minutes.

[00189] In another method of the invention, the analgesic dose of levorphanol or a pharmaceutically acceptable salt thereof for a human adult through intravenous patient controlled analgesia, is between about 0.25 mg and about 3 mg every 3 to 20 minutes; or between about 0.15 mg and about 3 mg every 3 to 20 minutes; or between about 0.01 mg and about 3 mg every 3 to 20 minutes.

[00190] The term "administration concurrently" refers to the administration in subjects of: i) a single composition containing both μ -opioid receptor agonist and levorphanol; or ii) the administration of each such opioid agonists as separate compositions and/or delivered by separate routes within a short enough period of time that effective result is equivalent to that obtained when both such opioid agonists are administered as a single composition; or iii) "intermittent administration" of levorphanol to treat "breakthrough pain" in subjects who are receiving "around the clock" analgesic treatment with μ -opioid receptor agonist.

[00191] The term "around the clock" as used herein with respect to the use of μ -opioid receptor agonists refers to the regular, approximately regular or continuous of use of a μ -opioid receptor agonist. Nonlimiting examples, depending on the duration of action of the μ -opioid receptor agonist, the mode of delivery and the pharmaceutical formulation are immediate release formulations about every 4, 6, 8, 12 or 24 hours; controlled release oral formulations about every 12 or 24 hours; controlled release epidural formulations every 24 to 72 hours; transdermal formulations every 1, 3 or 7 days.

[00192] The term "intermittent administration" as used herein with respect to the use of levorphanol refers to its occasional, periodic or non-scheduled use in subjects. Nonlimiting examples are the use of levorphanol 1 to 4 times per day, as required, to treat moderate to severe pain in subjects with transitory exacerbations of pain who are receiving an around the clock μ -opioid receptor agonist.

[00193] The present invention anticipates the use of more than one μ -opioid receptor agonist, co-administered with levorphanol. In one embodiment, the μ -opioid receptor agonists consist of morphine and oxycodone, coadministered with levorphanol. In another embodiment, the μ -opioid receptor agonists consist of hydromorphone and oxycodone, coadministered with levorphanol. In yet another embodiment, the μ -opioid receptor agonists consist of transdermal sufentanil and oral morphine, coadministered with levorphanol.

[00194] The term “breakthrough pain” as used herein refers to the transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain. Breakthrough pain may be a consequence of end-of dose failure (e.g., reduced μ -opioid agonist CNS concentrations towards the end of the dosing interval) or incident pain (e.g., a precipitating event causing pain such as voluntary or involuntary activity) or idiopathic. Breakthrough pain may occur in patients with various types of pain, including cancer pain, non-malignant pain and neuropathic pain.

[00195] The term “controlled release” as used herein is intended to distinguish it from immediate release dosage forms. Controlled release means a formulation or composition intended for any route of administration, including oral, buccal, rectal, transdermal, epidural, intramuscular, subcutaneous, inhaled and the like, which is prepared in such a manner as to allow for delayed, gradual, modulated and /or prolonged release of the μ -opioid receptor agonist and/or levorphanol. As used herein, controlled release is interchangeable with “extended release”, “sustained release”, “pulsatile release”, “modified release”, “depot” and the like.

[00196] It is contemplated that the present invention may be used alone or in combination with other drugs to provide additive, complementary, or synergistic therapeutic effects, including other NSAIDs, COX-2 selective inhibitors, acetaminophen, tramadol, local anesthetics, beta adrenergic agonists, alpha-2 agonists, selective prostanoid receptor antagonists, cannabinoid receptor agonists, NMDA receptor antagonists, neuronal nicotinic receptor agonists, calcium channel antagonists, sodium channel blockers, superoxide dismutase mimetics, p38 MAP kinase inhibitors, TRPV1 agonists, antiepileptics, and any other drugs that can be shown by a person proficient in the art to prevent or treat pain. The drug being used in combination therapy with the present invention can be administered by any route, including parenterally, orally, topically, transdermally, sublingually, and the like.

Determination of Analgesic Activity

[00197] The analgesic effects of the compositions of the present invention can be evaluated in one or more of the tests described below:

Rat Tail Flick Test

[00198] The tail flick test was first described by D'Amour and Smith (1941), and remains essentially unchanged in application. (See generally D'Amour, F.E. and Smith, D.L., "A method for determining loss of pain sensation", *J. Pharmacol. Exp. Therap.*, 72:74-79(1941); Dewey, D.L. and Harris, L.S., The Tail-flick test. In: S. Ehrenpreis and A. Neidle (Eds.), *Methods in Narcotic Research*, Marcel Dekker, Inc., New York, 1975, pp. 101-109; and Dubner, R. and Ren, K., "Assessing transient and persistent pain in animals." In: P.D. Wall and R. Melzack (Eds.), *Textbook of Pain*, Churchill Livingstone, London, 1999, pp. 359-369). Quite simply, the tail of a rat or mouse is exposed to radiant heat, and the latency to withdraw is determined. The basal heat intensity is set so that naïve rats withdraw their tails within 2 to 3 sec. A cut-off latency of 10 sec (*i.e.*, 3 to 4 times basal control value) is commonly employed to prevent tissue damage. An alternative to using radiant heat is to dip the tail into a water bath maintained at a fixed temperature, usually in the moderately noxious range of about 52°C or 55°C. One advantage of a water bath is that the temperature is kept constant.

[00199] The tail-flick test is considered to be very robust in that weak analgesic agents are not detected by this test. In contrast, it is considered highly selective. There is a high degree of correlation between drugs that are identified as antinociceptive in the tail-flick test and clinically active analgesic agents. It is especially predictive of rank-order of potency of opioid-type analgesic agents, and the clinically effective dose of a novel opioid may be predicted by the relative potency of the drug to a known substance, such as morphine, based on this assay.

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Importantly, agents that are sedating and may produce a positive response in the writhing test or hot plate test do not show antinociceptive activity in the tail-flick test. It is even possible to perform the tail-flick test in lightly anesthetized animals.

[00200] Data obtained from the rat tail-flick test conform to a graded dose-response curve. The raw tail withdrawal latencies are converted to a %MPE (% maximal possible effect) by the formula:

$$\% \text{ MPE} = 100 \times (\text{test latency} - \text{basal latency}) / (\text{cut-off} - \text{basal latency}).$$

[00201] This formula constrains the data to fit between 0% MPE and 100 % MPE. This allows the generation of dose-response curves and the calculation of ED₅₀ values (50% effective doses) with attendant confidence intervals. These calculations then allow for the determination of relative potencies of different drugs and allow for the isobolographic determination of possible synergistic effects. Instances where the test latency is less than the basal latency produces a negative % MPE, which is meaningless unless one is measuring hyperalgesia. By convention, these values are set to 0 % MPE when the expected drug effect is antinociception or no activity.

Kim and Chung Peripheral Neuropathy Model

[00202] The method of Kim and Chung is used to evaluate the potential analgesic properties of one or more compounds in a model of peripheral mononeuropathy. (See Kim, S.H. & Chung, J.M. "An experimental peripheral neuropathy produced by segmental nerve ligation in the rat," *Pain* 50:355-363 (1992); Hargreaves, K., *et al.*, "A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia," *Pain* 32:77-88 (1988); Lynn, B. & Carpenter, S.E. "Primary afferent units from the hairy skin of the rat hind limb," *Brain Research*

238:29-43 (1982)). Following baseline assessment of mechanical, thermal, and cold allodynia over 2 days, a peripheral mononeuropathy is induced by tight ligation of the left L5 and L6 spinal nerves under aseptic conditions. The animals are allowed to recover from surgery for six days before the behavioural testing is recommenced. Typically, behavioral testing is resumed on day 7 post-operatively and repeated on days 9 and 11 to monitor the development of allodynia and/or hyperalgesia. Tests with the putative analgesic(s) are carried out on or about day 12 (the time-point corresponding to maximal behavioural changes).

[00203] The following tests are typically performed in combination depending on the parameters to be assessed. A minimum period of 5 minutes is allowed between each type of test (or repeat challenges to the same paw) to reduce the risk of sensitization. Mechanical allodynia test: The animal is placed in a wire mesh cage, and a series of Von Frey filaments are applied to the plantar surface of the hind paw, from below. The filaments are applied in ascending order (starting with the weakest force), and the withdrawal threshold for both the ipsilateral and contralateral hind paws is evaluated. The withdrawal threshold is defined as being the lowest force of two or more consecutive Von Frey filaments to elicit a reflex withdrawal response (*i.e.*, a brief paw flick). Thermal hyperalgesia test: Rats are placed in clear plastic chambers with a glass floor and allowed a short period to acclimatize to their environment prior to testing (approximately 2 minutes). The animals are then challenged with a radiant infrared heat source, directed at the plantar surface of their hind paw from below, and the withdrawal latency calculated for both the ipsilateral and contralateral hind paws. Cold allodynia test: Rats are placed on a metal platform submerged approximately 1 cm below the surface of iced water (approximately 4°C), such that the hairy and glabrous skin of the animals feet are in contact with the cold water. Following an acclimatization period of approximately 30 seconds, the suspended paw elevation time (SPET) for the ipsilateral hind paw (that is, the total, accumulative length of

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time the animal holds its affected hind paw out of the water in a defensive posture) is measured during a 20 second challenge.

[00204] Standard statistical methods are employed to evaluate test substance related effects. Data are analyzed for homogeneity and either parametric or non-parametric methods applied as appropriate.

Carrageenan-Induced Inflamed Paw Model

[00205] Models of inflammation that produce more persistent pain include the injection of carrageenan into the footpad of the limb; the potential analgesic and/or anti-inflammatory properties of putative analgesics substances can be evaluated in this model. See generally Bhalla T.N. & Tangri, K.K. "The time course of the carrageenan-induced oedema of the paw of the rat." *J. Pharm. Pharmacol.* 22:721 (1970); Randall, L.O. & Selitto, J.J., "A method for measurement of analgesic activity on inflamed tissue," *Arch. Int. Pharmacodyn. Ther.* 111:409-419 (1957); Hargreaves, K., *et al.* "A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia." *Pain* 32:77-88 (1988).

[00206] Typically, rats are handled and acclimatized to the behavioral testing equipment over a minimum of 2 days prior to testing. Behavioral tests are performed on all rats on the day prior to dosing to establish baseline values, and the animals are randomized into treatment groups based on these pre-dose responses. An assessment of the inflammatory agent (carrageenan) is performed prior to the main study, using the chosen behavioral tests. On the day of dosing, an inflammatory response is induced in the left hind paw of each rat by an intraplantar injection (approx. 0.05 mL) of carrageenan (0.6% w/v), under brief anesthesia. The test substance, reference substance, or vehicle is generally administered 30 minutes prior to carrageenan administration for oral dosing.

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- [00207] The following tests may be performed. A minimum period of 5 minutes is allowed between each type of test (or repeat challenges to the same paw) to reduce the risk of sensitization.
- [00208] Paw Volume: Each animal is gently restrained, their hind limb extended, and the paw placed in the pre-filled chamber of a Digital Plethysmometer. The paw volume is then calculated based on the volume of liquid displaced in the chamber, for both the ipsilateral and contralateral hind paws.
- [00209] Mechanical hyperalgesia test: Each rat is gently restrained, their hind limb extended, and the paw placed lightly on the Randall-Selitto device. A progressively increasing pressure is then applied to the dorsal surface of the paw via a blunt peg attached to a weight level, and the withdrawal threshold calculated for both the ipsilateral and contralateral hind paws. The maximum pressure applied is about 250 g. The withdrawal threshold is defined as the minimum force (in grams) required to elicit a reflex withdrawal response. Typical end points are a struggle response, paw withdrawal or a squeak response.
- [00210] Thermal hyperalgesia test: Rats are placed in clear plastic chambers with a glass floor and allowed a short period to acclimatize to their environment prior to testing (approximately 2-5 minutes). The animals are then challenged with a radiant infrared heat source, directed at the plantar surface of their hind paw from below, and the withdrawal latency calculated for both the ipsilateral and contralateral hind paw
- [00211] Standard statistical methods are employed to evaluate test substance related effects. Data are analyzed for homogeneity and either parametric or non-parametric methods applied.
- [00212] The included examples are illustrative but not limiting of the methods and composition of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Acute Postsurgical Pain in Humans

[00213] The increased therapeutic benefits associated with co-administration of a μ -opioid receptor agonist and levorphanol may be demonstrated in single dose randomized, double-blind, controlled studies comparing subanalgesic and analgesic doses of a μ -opioid receptor agonist, given alone; subanalgesic and analgesic doses of levorphanol, and coadministration of subanalgesic doses of a μ -opioid receptor agonist plus levorphanol in patients experiencing moderate or severe postsurgical pain *e.g.*, pain following third molar extraction surgery, hip or knee arthroplasty, bunionectomy, abdominal hysterectomy and renal colic. Typically, patients are washed off their analgesic and anesthetic to allow for pain of moderate to severe intensity to return. Once a stable baseline pain score is established, patients are randomized to treatment with a single dose of one of the test treatments and placebo. Pain intensity and pain relief assessments are recorded at Baseline (0 hour), 15, 30 and 45 minutes and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours after administration of study medication using categorical and visual analog scales self-rating scales. The onset of action (time to confirmed perceptible pain relief) and the time to meaningful pain relief can be assessed using the two stopwatch method, and the magnitude and duration of analgesia can be assessed by calculating total pain relief (TOTPAR), sum of pain intensity difference (SPID), sum of pain relief intensity difference (SPRID), time to first rescue analgesic use, peak pain intensity difference (PPID), peak pain relief (PPR) and patient global evaluation. Sample sizes in the studies are sufficient to demonstrate the increased therapeutic benefit of coadministration involving subanalgesic doses of a μ -opioid receptor agonist plus levorphanol.

Chronic Pain of Osteoarthritis

[00214] The increased therapeutic benefits associated with co-administration of a μ -opioid receptor agonist and levorphanol may be demonstrated in repeated

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dose randomized, double-blind, controlled studies comparing subanalgesic and analgesic doses of a μ -opioid receptor agonist, given alone; subanalgesic and analgesic doses of levorphanol, and coadministration of subanalgesic and/or analgesic doses of a μ -opioid receptor agonist plus levorphanol in patients experiencing moderate or severe of pain of oseteoarthritis (OA). Typically, patients who meet the American College of Rheumatology criteria for knee and/or hip OA are washed off their analgesics for 2 to 7 days to allow for pain of moderate to severe intensity to return. Once a stable baseline pain score is established, patients are randomized to treatment, usually for a period of four to 12 weeks. Pain, joint stiffness and physical function can be measured with a multidimensional instrument, such as the WOMAC, quality of life with the SF-12 or SF-36 and adverse events with a non-directed questionnaire at baseline and at post-baseline return visits. Response to pain, stiffness, physical function, quality of life and adverse events are calculated as change from baseline and compared between treatments. Sample sizes in the studies are sufficient to demonstrate the increased therapeutic benefit of coadministration involving a μ -opioid receptor agonist plus levorphanol.

DRAWINGS

[00215] In order that the invention may be readily understood and put into practical effect, particular preferred embodiments will now be described by way of example with reference to the accompanying drawings in which:

[00216] Figure 1 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination, for data generated 30 minutes after injection. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components

and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value if found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00217] Figure 2 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 45 minutes after injection. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value if found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00218] Figure 3 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 60 minutes after injection. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value if found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00219] Figure 4 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 90 minutes after injection. Whereas levorphanol and the combination of levorphanol with morphine produce a full dose-dependent antinociceptive effect, the effect of morphine is diminishing at this time-point, as shown by the decrease in slope of the dose-response curve and the maximal endpoint is below 50% effect. The dose-response curve for the mixture is to the left of levorphanol alone, indicating potentiation of antinociceptive activity.

[00220] Figure 5 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 120 minutes after injection. Whereas levorphanol and the combination of levorphanol with morphine produce a full dose-dependent antinociceptive effect, the effect of morphine alone is very low. The dose-response curve for the mixture is to the left of levorphanol alone, indicating potentiation of antinociceptive activity.

[00221] Figure 6 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.1 mg/kg of levorphanol plus 0.1 mg/kg of morphine, 0.3 mg/kg levorphanol and 1.0 mg/kg morphine to Sprague-Dawley rats.

[00222] Figure 7 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.3 mg/kg of levorphanol plus 0.3 mg/kg of morphine, 0.6 mg/kg levorphanol, 1.0 mg/kg levorphanol, 3.0 mg/kg morphine and 6.0 mg/kg morphine to Sprague-Dawley rats.

[00223] Figure 8 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 1.0 mg/kg of levorphanol plus 1.0 mg/kg of morphine, 1.0 mg/kg levorphanol, 3.0

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mg/kg levorphanol, 6.0 mg/kg morphine and 10.0 mg/kg morphine to Sprague-Dawley rats.

[00224] Figure 9 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 1, 3, 6 and 10 mg/kg of morphine to Sprague-Dawley rats.

[00225] Figure 10 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.3, 0.6, 1 and 3 mg/kg of levorphanol to Sprague-Dawley rats.

[00226] Figure 11 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous co-administration of 0.1 mg/kg of levorphanol plus 0.1mg/kg of morphine, 0.3 mg/kg of levorphanol plus 0.3mg/kg of morphine, 1.0 mg/kg of levorphanol plus 1.0 mg/kg of morphine, to Sprague-Dawley rats.

[00227] Figure 12 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination, for data generated 30 minutes after injection. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value is found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00228] Figure 13 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 45 minutes after injection. The inset shows the isobologram indicative of a synergistic

interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value is found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00229] Figure 14 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 60 minutes after injection. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value is found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction.

[00230] Figure 15 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 90 minutes after injection. Whereas levorphanol and the combination of levorphanol with morphine produce a full dose-dependent antinociceptive effect, the effect of morphine is diminishing at this time-point, as shown by the decrease in slope of the dose-response curve and the maximal endpoint of only 63 %MPE. The dose-response curve for the mixture is to the left of levorphanol alone, indicating potentiation of antinociceptive activity.

[00231] Figure 16 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of dose (i.e., the antinociceptive dose-response curves) for levorphanol, morphine and the combination for data generated 120 minutes after injection. Whereas levorphanol and the combination of levorphanol with morphine produce a full dose-dependent antinociceptive effect, the effect of morphine is diminishing at this time-point, as shown by the decrease in slope of the dose-response curve and the maximal endpoint of only 65 %MPE. The dose-response curve for the mixture is to the left of levorphanol alone, indicating potentiation of antinociceptive activity.

[00232] Figure 17 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous administration of 0.1 mg/kg of levorphanol plus 0.1 mg/kg of morphine, 0.3 mg/kg levorphanol and 1.0 mg/kg morphine to Sprague-Dawley rats.

[00233] Figure 18 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous administration of 0.3 mg/kg of levorphanol plus 0.3 mg/kg of morphine, 0.5 mg/kg levorphanol, 1.0 mg/kg levorphanol, 3.0 mg/kg morphine and 6.0 mg/kg morphine to Sprague-Dawley rats.

[00234] Figure 19 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous administration of 1.0 mg/kg of levorphanol plus 1.0 mg/kg of morphine, 1.0 mg/kg levorphanol, 3.0 mg/kg levorphanol, 6.0 mg/kg morphine and 10.0 mg/kg morphine to Sprague-Dawley rats.

[00235] Figure 20 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous administration of 1, 3, 6 and 10 mg/kg of morphine to Sprague-Dawley rats.

[00236] Figure 21 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous administration of 0.3, 0.5, 1 and 3 mg/kg of levorphanol to Sprague-Dawley rats.

- [00237] Figure 22 shows the degree of antinociception (%MPE) on the hot-plate latency test as a function of time following subcutaneous co-administration of 0.1 mg/kg of levorphanol plus 0.1mg/kg of morphine, 0.3 mg/kg of levorphanol plus 0.3mg/kg of morphine, 1.0 mg/kg of levorphanol plus 1.0 mg/kg of morphine, to Sprague-Dawley rats.
- [00238] Figure 23 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.075 mg/kg of fentanyl and subcutaneous co-administration of 0.075 mg/kg of fentanyl plus 0.3mg/kg of levorphanol to Sprague-Dawley rats.
- [00239] Figure 24 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.4 mg/kg of hydromorphone and subcutaneous co-administration of .4 mg/kg of hydromorphone plus 0.3mg/kg of levorphanol to Sprague-Dawley rats.
- [00240] Figure 25 shows the degree of antinociception (%MPE) on the tail-flick latency test as a function of time following subcutaneous administration of 0.6 mg/kg of oxycodone and subcutaneous co-administration of . 0.6 mg/kg of oxycodone plus 0.3mg/kg of levorphanol to Dark Agouti rats.

EXAMPLE 1

MATERIALS AND METHODS

Drugs

- [00241] The test substance, morphine sulfate (morphine) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.5, 1.5, 3 and 5 mg/mL.
- [00242] The test substance, Levorphanol tartrate dihydrate (Levorphanol) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.15, 0.3, 0.5 and 1.5 mg/mL.

[00243] All formulations were freshly prepared on the day of dosing and protected from light until use.

Animals

[00244] Male Sprague-Dawley rats, within the weight range of 100-200 g and approximate age of 5 weeks were utilized. The animals were housed in groups of up to 5 in solid-bottomed plastic cages with sawdust or paper bedding. The rooms were illuminated by fluorescent lights set to give a 12 h light-dark cycle, air-conditioned and the air temperature was set at $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Rats had unlimited access to food and water. Each animal was arbitrarily allocated a unique identification number and identified by a waterproof tail mark. The rats were randomly allocated to the treatment groups prior to dosing based on the pre-dose baseline values for the tail flick test.

Dosing

[00245] The dose volume for all treatments was 2 mL/kg. The vehicle for Levorphanol and Morphine was 0.9 % w/v sodium chloride. Each rat received a single subcutaneous injection. Dosing solutions were encoded so that the observer did not know the identity of the treatment groups. Animals were weighed prior to testing, on the same day as the administration of substances.

Conversion of levorphanol and morphine doses from salt formulation to represent free base content and moles					
Levorphanol $\text{C}_2\text{H}_6\text{O}_6 \cdot 2\text{H}_2\text{O}$ (58%FB)			Morphine $\text{SO}_4 \cdot 5\text{H}_2\text{O}$ (75%FB)		
MW = 443.49			MW = 758.77		
Salt	Free Base	μmoles	Salt	Free Base	μmoles
0.3 mg/kg	0.17 mg/kg	0.67 $\mu\text{moles/kg}$	1 mg/kg	0.75 mg/kg	2.64 $\mu\text{moles/kg}$
0.6 mg/kg	0.35 mg/kg	1.34 $\mu\text{moles/kg}$	3 mg/kg	2.26 mg/kg	7.91 $\mu\text{moles/kg}$
1 mg/kg	0.58 mg/kg	2.24 $\mu\text{moles/kg}$	6 mg/kg	4.52 mg/kg	15.8 $\mu\text{moles/kg}$
3 mg/kg	1.74 mg/kg	6.72 $\mu\text{moles/kg}$	10 mg/kg	7.5 mg/kg	26.4 $\mu\text{moles/kg}$

Assessment of Antinociception

[00246] The rats were acclimatized for at least 3 days before study commencement. On 3 separate occasions prior to the start of the experiment, each animal was handled in a manner which acclimatized them to the behavioural testing environment and equipment. Pre-dose baseline values were calculated as the mean of the latter 2 test values.

[00247] Each rat was lightly held on the surface of the tail flick apparatus (Ugo Basile, Italy), so that its tail was positioned directly over the infrared source. The infrared source was then applied to a small area on the ventral surface of the tail. Activation of the infrared source simultaneously activated a timer, which automatically registered the time taken to deflect (withdraw or flick) the tail. The tail flick latency was noted for each animal. The infrared intensity was set at IR30 and the maximum length of exposure to the IR source was 10 s. Non-responding animals were therefore allocated a withdrawal latency of 10 s. Tail flick tests were performed at approximately 30, 45, 60, 90 and 120 min post-dose.

Data Analysis

[00248] A 10-second cut-off value was employed to avoid tissue damage. The data were converted to % Maximal Possible Effect (% MPE; or % Antinociception) based on the formula: $100 \times (\text{test latency} - \text{baseline latency}) / (10 \text{ sec} - \text{baseline latency})$. This formula corrects for individual variations among animals and allows for the generation of proper dose-response curves. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 10 sec indicates a 100% effect. Dose response curves were generated for the 4 observation time points and the A_{50} (50% MPE dose) was calculated.

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Results

[00249] The time-course antinociceptive activity as % MPE \pm SEM for all treatment groups in the rat tail-flick assay is given in the Table below and Figures 9 & 10.

Levorphanol dose is given as mg/kg, free base					
	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
0.174	21.04 \pm 9.21	9.22 \pm 3.33	5.17 \pm 2.05	6.11 \pm 1.84	4.66 \pm 2
0.35	40.26 \pm 9.7	30.68 \pm 8	16.81 \pm 9.07	7.47 \pm 2.08	5.34 \pm 2.17
0.58	90.71 \pm 5.97	97.16 \pm 2.69	88.68 \pm 5.85	44.66 \pm 6.41	21.59 \pm 4.85
1.74	100 \pm 0	100 \pm 0	100 \pm 0	86.36 \pm 4.37	55.58 \pm 7.88
Morphine dose is given as mg/kg, free base					
	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
0.75	10.06 \pm 4.4	5.05 \pm 1.51	3.17 \pm 1.3	10.23 \pm 3.26	6.74 \pm 2.45
2.26	30.31 \pm 9.01	13.92 \pm 5.17	14.45 \pm 2.58	12.19 \pm 3.41	8.62 \pm 2.83
4.52	72.8 \pm 13.15	65.13 \pm 13.36	60.63 \pm 13.45	43.69 \pm 9.97	27.65 \pm 7.06
7.5	97.88 \pm 2.01	97.12 \pm 2.73	90.58 \pm 5.17	28.78 \pm 5.04	11.59 \pm 3.48

[00250] Both levorphanol and morphine produced a dose-dependent and time-dependent antinociceptive activity over the full range of doses administered at 30, 45 and 60 minutes after injection.

[00251] The data indicating A_{50} values are indicated in the Table below.

A_{50} values as mg/kg, free base					
Treatment	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
Levorphanol	0.35 \pm 0.088	0.40 \pm 0.072	0.047 \pm 0.083	0.72 \pm 0.11	1.66 \pm 0.65
Morphine	2.56 \pm 0.59	3.09 \pm 0.67	3.38 \pm 0.76	NA*	NA*

EXAMPLE 2

MATERIALS AND METHODS

Drugs

[00252] The test substance, morphine sulfate (morphine) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions 0.05, 0.15 and 0.5 mg/mL.

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[00253] The test substance, Levorphanol tartrate dihydrate (Levorphanol) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.15, 0.5 and 1.5 mg/mL.

[00254] All formulations were freshly prepared on the day of dosing and protected from light until use.

Animals

[00255] Male Sprague-Dawley rats, within the weight range of 100-200 g and approximate age of 5 weeks were utilized. The animals were housed in groups of up to 5 in solid-bottomed plastic cages with sawdust or paper bedding. The rooms were illuminated by fluorescent lights set to give a 12 h light-dark cycle, air-conditioned and the air temperature was set at $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Rats had unlimited access to food and water. Each animal was arbitrarily allocated a unique identification number and identified by a waterproof tail mark. The rats were randomly allocated to the treatment groups prior to dosing based on the pre-dose baseline values for the tail flick test.

Dosing

[00256] The combination doses to be investigated in the current study are as follows: a) 0.1 mg/kg morphine plus 0.1 mg/kg Levorphanol; b) 0.3 mg/kg Morphine plus 0.3 mg/kg Levorphanol; c) 1 mg/kg Morphine plus 1 mg/kg Levorphanol.

[00257] The dose volume for all treatments was 2 mL/kg per drug. The vehicle for Levorphanol and Morphine was 0.9 % w/v sodium chloride. Each rat received a subcutaneous injection of morphine, immediately followed by a subcutaneous injection of levorphanol.

[00258] . Dosing solutions were encoded so that the observer did not know the identity of the treatment groups. Animals were weighed prior to testing, on the same day as the administration of substances.

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Conversion of levorphanol and morphine doses from salt formulation to represent free base content and moles		
Levorphanol $C_{18}H_{26}O_6 \cdot 2H_2O$ (58%FB)		Morphine $SO_4 \cdot 5H_2O$ (75%FB)
MW = 443.49		MW = 758.77
Levorphanol + Morphine Salt	Free Base	Mmoles
0.1 mg/kg + 0.1 mg/kg = 0.2 mg/kg	0.057 mg/kg + 0.075 mg/kg = 0.132 mg/kg	0.224 μ moles/kg + 0.264 μ moles/kg = 0.488 μ moles/kg
0.3 mg/kg + 0.3 mg/kg = 0.6 mg/kg	0.17 mg/kg + 0.23 mg/kg = 0.4 mg/kg	0.67 μ moles/kg + 0.79 μ moles/kg = 1.46 μ moles/kg
1 mg/kg + 1 mg/kg = 2 mg/kg	0.57 mg/kg + 0.75 mg/kg = 1.32 mg/kg	2.24 μ moles/kg + 2.64 μ moles/kg = 4.88 μ moles/kg

Assessment of Antinociception

[00259] The rats were acclimatized for at least 3 days before study commencement. On 3 separate occasions prior to the start of the experiment, each animal was handled in a manner which acclimatized them to the behavioural testing environment and equipment. Pre-dose baseline values were calculated as the mean of the latter 2 test values.

[00260] Each rat was lightly held on the surface of the tail flick apparatus (Ugo Basile, Italy), so that its tail was positioned directly over the infrared source. The infrared source was then applied to a small area on the ventral surface of the tail. Activation of the infrared source simultaneously activated a timer, which automatically registered the time taken to deflect (withdraw or flick) the tail. The tail flick latency was noted for each animal. The infrared intensity was set at IR30 and the maximum length of exposure to the IR source was 10 s. Non-responding animals were therefore allocated a withdrawal latency of 10 s. Tail flick tests were performed at approximately 30, 45, 60, 90 and 120 min post-dose.

Data Analysis

[00261] A 10-second cut-off value was employed to avoid tissue damage. The data were converted to % Maximal Possible Effect (% MPE; or % Antinociception) based on the formula: $100 \times (\text{test latency} - \text{baseline latency}) / (10 \text{ sec} - \text{baseline})$

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latency). This formula corrects for individual variations among animals and allows for the generation of proper dose-response curves. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 10 sec indicates a 100% effect. Dose response curves were generated for the 4 observation time points and the A_{50} (50% MPE dose) was calculated.

[00262] The interaction between levorphanol and morphine was examined by isobolographic analysis. The statistical evaluation by means of isobolographic methods was described in detail by Tallarida and colleagues (1989; 1990) and has been applied extensively by Ossipov and colleagues (1990a, b, c; 1997). Dose-effect curves were constructed for systemic levorphanol, morphine and a 1:1 fixed ratio of levorphanol to morphine. For each drug or drug combination, the A_{50} dose (i.e., dose calculated to produce 50 %MPE) and its associated variances and the 95% confidence intervals (95% CI) in terms of total dose were calculated from the log-dose-response curves. The confidence intervals were then arithmetically arranged around the A_{50} by the formula $\text{Ln}(10) \times A_{50} \times \text{standard error of log}(A_{50})$. This transformation is necessary for subsequent statistical calculations of the isobolographic analysis. Where only a single drug was given, the "total dose" was the dose of the drug alone; otherwise, it represented the total amount of levorphanol and morphine that is administered to the animal. A theoretical additive A_{50} is calculated for the drug combination. If the relative potency of the theoretical additive A_{50} relative to the actual A_{50} , along with the associated variances, obtained experimentally for the mixture is significantly (P less or equal to 0.05) greater than 1, a synergistic interaction is indicated. A simple additive interaction is indicated when the theoretical and experimental A_{50} values are not significantly different from each other. In order to minimize artifact in statistical calculations based on inactive components, the doses were converted to the free-base form for the statistical evaluation and determination of A_{50} values and

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subsequent isobolographic analysis. The corresponding molecular equivalent is also provided for additional information.

[00263]

Results

[00264] The time-course antinociceptive activity as % MPE \pm SEM for all treatment groups in the rat tail-flick assay is given in the Table below and Figures 6, 7, 8 & 11.

Mixture of Levorphanol and Morphine is Given As Total Dose in mg/kg, free base					
	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
0.132	17.79 \pm 6.59	7.61 \pm 2.84	12.06 \pm 3.32	11.7 \pm 3.38	4.67 \pm 2.91
0.40	96.34 \pm 3.47	94.2 \pm 5.33	88.56 \pm 7.71	44.73 \pm 7.05	19.86 \pm 4.99
1.32	100 \pm 0	100 \pm 0	100 \pm 0	88.9 \pm 6.39	69.72 \pm 6.64

[00265] The combination of levorphanol and morphine produced a dose-dependent and time-dependent antinociceptive activity over the full range of doses administered at 30, 45 and 60 minutes after injection.

[00266] The levorphanol-morphine combination produced dose-dependent and time-dependent antinociceptive activity over the full range of doses administered at 30, 45 and 60 minutes after injection. The antinociceptive effect of morphine did not reach 50% MPE at 90 minutes, and morphine was virtually without effect at 120 minutes. Consequently, isobolographic analysis was only possible at the initial 3 time points. At 30, 45 and 60 minutes after injection, the antinociceptive effect of the combination of levorphanol and morphine was determined to be synergistic. In spite of the loss of antinociceptive activity of morphine at 90 and 120 minutes, there is demonstration of synergy because the dose effect curve for the combination is shifted to the left of that for levorphanol alone.

[00267] The data indicating A_{50} values, theoretical additive A_{50} and the indication of synergy are indicated in the following Table.

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A_{50} values as mg/kg, free base					
Treatment	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
Levorphanol	0.35 ± 0.088	0.40 ± 0.072	0.047 ± 0.083	0.72 ± 0.11	1.66 ± 0.65
Morphine	2.56 ± 0.59	3.09 ± 0.67	3.38 ± 0.76	NA*	NA*
Mixture	0.22 ± 0.068	0.26 ± 0.066	0.26 ± 0.067	0.43 ± 0.091	0.78 ± 0.23
Additive A_{50} (Theoretical)	0.68 ± 0.15	0.79 ± 0.13	0.92 ± 0.15	1.61 ± 0.26	3.85 ± 1.58
Finding	Synergy	Synergy	Synergy	Synergy	Synergy

[00268] The antinociceptive dose-response curves for levorphanol, morphine and the combination are shown for data generated 30, 60, 90 and 120 minutes after injection are shown in Figures 1 to 5, respectively. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value is found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction. Additivity would be indicated if the A_{50} point for the mixture would fall within the confidence limits of the theoretical additive point. On the dose-response curve, additivity would be suggested by finding the dose-response curve for the drug combination between those of the 2 components given alone, instead of being displaced in a leftward fashion.

EXAMPLE 3

MATERIALS AND METHODS

Drugs

[00269] The test substance, morphine sulfate (morphine) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.5, 1.5, 3 and 5 mg/mL.

[00270] The test substance, Levorphanol tartrate dihydrate (Levorphanol) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.15, 0.25, 0.5 and 1.5 mg/mL.

[00271] All formulations were freshly prepared on the day of dosing and protected from light until use.

Animals

[00272] Male Sprague-Dawley rats, within the weight range of 100-150 g and approximate age of 5 weeks were utilized. The animals were housed in groups of up to 5 in solid-bottomed plastic cages with sawdust or paper bedding. The rooms were illuminated by fluorescent lights set to give a 12 h light-dark cycle, air-conditioned and the air temperature was set at $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Rats had unlimited access to food and water. Each animal was arbitrarily allocated a unique identification number and identified by a waterproof tail mark. The rats were randomly allocated to the treatment groups prior to dosing based on the pre-dose baseline values for the tail flick test.

Dosing

[00273] The dose volume for all treatments was 2 mL/kg. The vehicle for Levorphanol and Morphine was 0.9 % w/v sodium chloride. Each rat received a single subcutaneous injection. Dosing solutions were encoded so that the

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observer did not know the identity of the treatment groups. Animals were weighed prior to testing, on the same day as the administration of substances.

Conversion of levorphanol and morphine doses from salt formulation to represent free base content and moles					
Levorphanol $C_{20}H_{27}NO_6 \cdot 2H_2O$ (58%FB) MW = 443.49			Morphine $SO_4 \cdot 5H_2O$ (75%FB) MW = 758.77		
Salt	Free Base	μ moles	Salt	Free Base	μ moles
0.3 mg/kg	0.17 mg/kg	0.67 μ moles/kg	1 mg/kg	0.75 mg/kg	2.64 μ moles/kg
0.5 mg/kg	0.29 mg/kg	1.12 μ moles/kg	3 mg/kg	2.26 mg/kg	7.91 μ moles/kg
1 mg/kg	0.58 mg/kg	2.24 μ moles/kg	6 mg/kg	4.52 mg/kg	15.8 μ moles/kg
3 mg/kg	1.74 mg/kg	6.72 μ moles/kg	10 mg/kg	7.5 mg/kg	26.4 μ moles/kg

Assessment of Antinociception

[00274] The rats were acclimatized for at least 3 days before study commencement. On 3 separate occasions prior to the start of the experiment, each animal was handled in a manner which acclimatized them to the behavioural testing environment and equipment. Pre-dose baseline values were calculated as the mean of the latter 2 test values.

[00275] Animals were tested by placing them on a hotplate maintained at 53 °C. Untreated animals respond to the heat by withdrawing or shaking of hind feet, sharp withdrawal or licking of fore feet, or attempting to escape by jumping. When any of these responses were observed, the treated animal was removed from the hotplate and the time taken to respond documented. The maximum length of exposure to the hotplate was 15 s. Non-responding animals were therefore allocated a response threshold of 15 s.

[00276] Each animal received either a single subcutaneous injection of test substance or vehicle. Hotplate tests will be performed at approximately 30, 45, 60, 90 and 120 min post-dose.

Data Analysis

[00277] A 15-second cut-off value was employed to avoid tissue damage. The data were converted to % Maximal Possible Effect (% MPE; or % Antinociception) based on the formula: $100 \times (\text{test latency} - \text{baseline latency}) / (15 \text{ sec} - \text{baseline latency})$. This formula corrects for individual variations among animals and allows for the generation of proper dose-response curves. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 15 sec indicates a 100% effect. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 15 sec indicates a 100% effect. Dose response curves were generated for the 4 observation time points and the A_{50} (50% MPE dose) was calculated.

Results

[00278] The time-course antinociceptive activity as % MPE \pm SEM for all treatment groups in the rat tail-flick assay is given in the Table below and Figures 20 & 21.

Levorphanol dose is given as mg/kg salt and free base (FB)					
mg/kg (mg/kg FB)	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
0.3 (0.174 FB)	35.71 \pm 8.24	59.05 \pm 10.65	94.32 \pm 2.85	100 \pm 0	35.71 \pm 8.24
0.5 mg/kg (0.29 FB)	32.89 \pm 11.09	54.67 \pm 7.87	83.72 \pm 6.74	100 \pm 0	32.89 \pm 11.09
1 mg/kg (0.58 FB)	37.34 \pm 9.74	28.5 \pm 5.35	85.18 \pm 7.48	100 \pm 0	37.34 \pm 9.74
3 mg/kg) 1.74 FB	19.42 \pm 7.15	16.42 \pm 3.79	68.87 \pm 9.46	91.44 \pm 3.37	19.42 \pm 7.15
Morphine dose is given as mg/kg salt and free base (FB)					
	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1 mg/kg (0.75 FB)	15.42 \pm 5.3	45.94 \pm 10.38	76.13 \pm 10.6	97.27 \pm 2.5	15.42 \pm 5.3
3 mg/kg (2.26 FB)	21.32 \pm 5.36	44.98 \pm 10.34	86.88 \pm 7.28	100 \pm 0	21.32 \pm 5.36
6 mg/kg (4.52 FB)	13.2 \pm 3.24	29.83 \pm 5.06	71.85 \pm 8.99	87.72 \pm 7.84	13.2 \pm 3.24
10 mg/kg (7.5 FB)	9.61 \pm 5.31	16.19 \pm 6.12	63.11 \pm 7.63	61.96 \pm 9.53	9.61 \pm 5.31

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[00279] Both levorphanol and morphine produced a dose-dependent and time-dependent antinociceptive activity over the full range of doses administered at 30, 45 and 60 minutes after injection.

[00280] The data indicating A_{50} values are indicated in the Table below.

Table B. A_{50} values as mg/kg, free base					
Treatment	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
Levorphanol	0.236 ± 0.053	0.257 ± 0.086	0.319 ± 0.086	0.488 ± 0.101	0.703 ± 0.205
Morphine	2.16 ± 0.510	1.90 ± 0.42	2.71 ± 0.577	4.41 ± 1.56	6.24 ± 2.45

EXAMPLE 4

MATERIALS AND METHODS

Drugs

[00281] The test substance, morphine sulfate (morphine) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions 0.05, 0.15 and 0.5 mg/mL.

[00282] The test substance, Levorphanol tartrate dihydrate (Levorphanol) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give solutions of 0.15, 0.5 and 1.5 mg/mL.

[00283] All formulations were freshly prepared on the day of dosing and protected from light until use.

Animals

[00284] Male Sprague-Dawley rats, within the weight range of 100-150 g and approximate age of 5 weeks were utilized. The animals were housed in groups of up to 5 in solid-bottomed plastic cages with sawdust or paper bedding. The rooms were illuminated by fluorescent lights set to give a 12 h light-dark cycle, air-conditioned and the air temperature was set at $21^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Rats had unlimited access to food and water. Each animal was arbitrarily allocated a unique

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identification number and identified by a waterproof tail mark. The rats were randomly allocated to the treatment groups prior to dosing based on the pre-dose baseline values for the tail flick test.

Dosing

[00285] The combination doses to be investigated in the current study are as follows: a) 0.1 mg/kg morphine plus 0.1 mg/kg Levorphanol; b) 0.3 mg/kg Morphine plus 0.3 mg/kg Levorphanol; c) 1 mg/kg Morphine plus 1 mg/kg Levorphanol.

[00286] The dose volume for all treatments was 2 mL/kg. The vehicle for Levorphanol and Morphine was 0.9 % w/v sodium chloride. Each rat received a subcutaneous injection of morphine, immediately followed by a subcutaneous injection of levorphanol. Dosing solutions were encoded so that the observer did not know the identity of the treatment groups. Animals were weighed prior to testing, on the same day as the administration of substances.

Conversion of levorphanol and morphine doses from salt formulation to represent free base content and moles		
Levorphanol $C_8H_{10}O_6 \cdot 2H_2O$ (58%FB)	Morphine $SO_4 \cdot 5H_2O$ (75%FB)	
MW = 443.49	MW = 758.77	
Levorphanol + Morphine Salt	Free Base	Mmoles
0.1 mg/kg + 0.1 mg/kg = 0.2 mg/kg	0.057 mg/kg + 0.075 mg/kg = 0.132 mg/kg	0.224 μ moles/kg + 0.264 μ moles/kg = 0.488 μ moles/kg
0.3 mg/kg + 0.3 mg/kg = 0.6 mg/kg	0.17 mg/kg + 0.23 mg/kg = 0.4 mg/kg	0.67 μ moles/kg + 0.79 μ moles/kg = 1.46 μ moles/kg
1 mg/kg + 1 mg/kg = 2 mg/kg	0.57 mg/kg + 0.75 mg/kg = 1.32 mg/kg	2.24 μ moles/kg + 2.64 μ moles/kg = 4.88 μ moles/kg

Assessment of Antinociception

[00287] The rats were acclimatized for at least 3 days before study commencement. On 3 separate occasions prior to the start of the experiment, each animal was handled in a manner which acclimatized them to the behavioural

testing environment and equipment. Pre-dose baseline values were calculated as the mean of the latter 2 test values.

[00288] Animals were tested by placing them on a hotplate maintained at 53 °C. Untreated animals respond to the heat by withdrawing or shaking of hind feet, sharp withdrawal or licking of fore feet, or attempting to escape by jumping. When any of these responses were observed, the treated animal was removed from the hotplate and the time taken to respond documented. The maximum length of exposure to the hotplate was 15 s. Non-responding animals were therefore allocated a response threshold of 15 s.

[00289] Each animal received a subcutaneous injection of morphine, immediately followed by a subcutaneous injection of levorphanol. Hotplate tests will be performed at approximately 30, 45, 60, 90 and 120 min post-dose.

Data Analysis

[00290] A 15-second cut-off value was employed to avoid tissue damage. The data were converted to % Maximal Possible Effect (% MPE; or % Antinociception) based on the formula: $100 \times (\text{test latency} - \text{baseline latency}) / (15 \text{ sec} - \text{baseline latency})$. This formula corrects for individual variations among animals and allows for the generation of proper dose-response curves. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 15 sec indicates a 100% effect. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 15 sec indicates a 100% effect. Dose response curves were generated for the 4 observation time points and the A_{50} (50% MPE dose) was calculated.

[00291] The interaction between levorphanol and morphine was examined by isobolographic analysis. The statistical evaluation by means of isobolographic methods was described in detail by Tallarida and colleagues (1989; 1990) and has been applied extensively by Ossipov and colleagues (1990a, b, c; 1997). Dose-

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effect curves were constructed for systemic levorphanol, morphine and a 1:1 fixed ratio of levorphanol to morphine (based on salt formulation). The dose ratio based on free base was 1:1.3, meaning that for every 1 mg of levorphanol that was injected, the rat received 1.3 mg of morphine. For each drug or drug combination, the A_{50} dose (i.e., dose calculated to produce 50 %MPE) and its associated variances and the 95% confidence intervals (95% CI) in terms of total dose were calculated from the log-dose-response curves. The confidence intervals were then arithmetically arranged around the A_{50} by the formula $\text{Ln}(10) \times A_{50} \times \text{standard error of } \log(A_{50})$. This transformation is necessary for subsequent statistical calculations of the isobolographic analysis. Where only a single drug was given, the "total dose" was the dose of the drug alone; otherwise, it represented the total amount of levorphanol and morphine that is administered to the animal. A theoretical additive A_{50} is calculated for the drug combination. If the relative potency of the theoretical additive A_{50} relative to the actual A_{50} , along with the associated variances, obtained experimentally for the mixture is significantly (P less or equal to 0.05) greater than 1, a synergistic interaction is indicated. A simple additive interaction is indicated when the theoretical and experimental A_{50} values are not significantly different from each other. In order to minimize artifact in statistical calculations based on inactive components, the doses were converted to the free-base form for the statistical evaluation and determination of A_{50} values and subsequent isobolographic analysis. The corresponding molecular equivalent is also provided for additional information.

[00292] Moreover, the interaction is also depicted in the form of an isobologram for each time point. The A_{50} value for levorphanol alone is placed on the abscissa, and the value for morphine is shown as the ordinate. A straight line connecting these points represents the line of additivity. For the drug combinations (Actual and theoretical additive), the A_{50} , along with the confidence intervals and expressed as total dose, is resolved into the components and plotted on the isobologram. In the present study, for every 1 part levorphanol there was 1.3

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parts morphine; therefore, the levorphanol contribution is derived as $1/(1 + 1.3)$ and the morphine contribution is derived as $1.3/(1+1.3)$, giving 0.43 and 0.57 respectively. Therefore, an A_{50} value of 0.21 mg/kg for the mixture consists of $0.43 \times 0.21 = 0.09$ mg/kg of levorphanol and 0.57×0.21 mg/kg = 0.12 mg/kg of morphine. This result is plotted as (0.09,0.12). If this point is significantly less than the theoretical additive point, and below the line of additivity, then a synergistic interaction is indicated.

Results

[00293] The time-course antinociceptive activity as % MPE \pm SEM for all treatment groups in the rat hotplate assay is given in the Table below and Figures 16, 17, 18, 19, 22.

Mixture of Levorphanol and Morphine is dose is given as mg/kg salt and free base (FB)					
	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
0.1 Lev + 0.1 Mor (0.058 + 0.075 FB)	35.02 \pm 5.85	74.9 \pm 8.38	100 \pm 0	35.02 \pm 5.85	74.9 \pm 8.38
0.3 Lev + 0.3 Mor (0.174 + 0.226 FB)	34.07 \pm 7.95	73.61 \pm 9.69	100 \pm 0	34.07 \pm 7.95	73.61 \pm 9.69
1 Lev + 1 Mor (0.58 + 0.75 FB)	18.02 \pm 4.24	70.45 \pm 8.82	99.54 \pm 0.44	18.02 \pm 4.24	70.45 \pm 8.82

[00294] The combination of levorphanol and morphine produced a dose-dependent and time-dependent antinociceptive activity over the full range of doses administered at 30, 45, 60, 90 and 120 minutes after injection. At each of these time-points, the antinociceptive effect of the combination of levorphanol and morphine was determined to be synergistic.

[00295] The data indicating A_{50} values, theoretical additive A_{50} and the indication of synergy are indicated in the following Table.

A_{50} values as mg/kg, free base					
Treatment	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
Levorphanol	0.236 \pm 0.053	0.257 \pm 0.086	0.319 \pm 0.086	0.488 \pm 0.101	0.703 \pm 0.205
Morphine	2.16 \pm 0.510	1.90 \pm 0.42	2.71 \pm 0.577	4.41 \pm 1.56	6.24 \pm 2.45
Mixture	0.200 \pm 0.066	0.208 \pm 0.081	0.285 \pm 0.064	0.346 \pm 0.078	0.457 \pm 0.126
Additive A_{50} (Theoretical)	0.475 \pm 0.095	0.516 \pm 0.151	0.636 \pm 0.157	0.988 \pm 0.192	1.42 \pm 0.384
Finding	Synergy	Synergy	Synergy	Synergy	Synergy

[00296] The antinociceptive dose-response curves for levorphanol, morphine and the combination are shown for data generated 30, 60, 90 and 120 minutes after injection are shown in Figures 12 to 16, respectively. The inset shows the isobologram indicative of a synergistic interaction. The A_{50} value for levorphanol is indicated on the abscissa and for morphine on the ordinate. A_{50} values for the mixture and the calculated theoretical additive A_{50} value are resolved into their levorphanol and morphine components and plotted on the isobologram. A theoretical line of additivity connects the values for levorphanol and morphine alone, and the theoretical additive A_{50} value is found on that line. The confidence intervals are also indicated. The data point for the actual mixture is found deep inside the isobologram and indicates a synergistic interaction. Additivity would be indicated if the A_{50} point for the mixture would fall within the confidence limits of the theoretical additive point. On the dose-response curve, additivity would be suggested by finding the dose-response curve for the drug combination between those of the 2 components given alone, instead of being displaced in a leftward fashion.

[00297] EXAMPLE 5

MATERIALS AND METHODS

Drugs

[00298] The test substance, fentanyl hydrochloride (fentanyl) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to a give solution of 0.0375 mg/mL.

[00299] The test substance, hydromorphone hydrochloride (hydromorphone) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to a give solution of 0.2 mg/mL.

[00300] The test substance, oxycodone hydrochloride (oxycodone) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to a give solution of 0.3 mg/mL.

[00301] The test substance, levorphanol tartrate (levorphanol) was formulated for dosing by dissolving a known amount in 0.9 % w/v sodium chloride to give a solution of 0.15 mg/mL.

[00302] All formulations were freshly prepared on the day of dosing and protected from light until use.

Animals

[00303] Male Sprague-Dawley rats, within the weight range of 100-150 g and approximate age of 5 weeks were utilized were used for evaluation of fentanyl and hydromorphone. Male Dark Agouti rats were utilized were used for oxycodone. The animals were housed in groups of up to 5 in solid-bottomed plastic cages with sawdust or paper bedding. The rooms were illuminated by fluorescent lights set to give a 12 h light-dark cycle, air-conditioned and the air temperature was set at $21\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$. Rats had unlimited access to food and water. Each animal was arbitrarily allocated a unique identification number and identified by a waterproof tail mark. The rats were randomly allocated to the treatment groups prior to dosing based on the pre-dose baseline values for the tail flick test.

Dosing

[00304] The dose volume for all treatments was 2 mL/kg. The vehicle for each test treatment was 0.9 % w/v sodium chloride. Each rat received a single subcutaneous injection of a subanalgesic dose of fentanyl, hydromorphone or oxycodone. For the combination with levorphanol, each animal received a subcutaneous injection of fentanyl, hydromorphone or oxycodone, immediately followed by a subcutaneous injection of a subanalgesic dose of levorphanol.

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Dosing solutions were encoded so that the observer did not know the identity of the treatment groups. Animals were weighed prior to testing, on the same day as the administration of substances.

Assessment of Antinociception

[00305] The rats were acclimatized for at least 3 days before study commencement. On 3 separate occasions prior to the start of the experiment, each animal was handled in a manner which acclimatized them to the behavioural testing environment and equipment. Pre-dose baseline values were calculated as the mean of the latter 2 test values.

[00306] Each rat was lightly held on the surface of the tail flick apparatus (Ugo Basile, Italy), so that its tail was positioned directly over the infrared source. The infrared source was then applied to a small area on the ventral surface of the tail. Activation of the infrared source simultaneously activated a timer, which automatically registered the time taken to deflect (withdraw or flick) the tail. The tail flick latency was noted for each animal. The infrared intensity was set at IR30 and the maximum length of exposure to the IR source was 10 s. Non-responding animals were therefore allocated a withdrawal latency of 10 s. Tail flick tests were performed at approximately 30, 45, 60, 90 and 120 min post-dose.

Data Analysis

[00307] A 10-second cut-off value was employed to avoid tissue damage. The data were converted to % Maximal Possible Effect (% MPE; or % Antinociception) based on the formula: $100 \times (\text{test latency} - \text{baseline latency}) / (10 \text{ sec} - \text{baseline latency})$. This formula corrects for individual variations among animals and allows for the generation of proper dose-response curves. A response latency equal to pre-treatment baseline indicates a 0% MPE and a response latency that reaches the cut-off of 10 sec indicates a 100% effect. Dose response curves were

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generated for the 4 observation time points and the A_{50} (50% MPE dose) was calculated.

Results

[00308] The time-course antinociceptive activity as % MPE \pm SEM for all treatment groups in the rat tail-flick assay is given in Figures 23-25.

[00309] At the selected doses, fentanyl, hydromorphone and oxycodone produced subanalgesic anti-nociception. When co-administered with a subanalgesic dose of levorphanol, subanalgesic doses of fentanyl, hydromorphone and oxycodone each produced robust and prolonged antinociception, indicating a synergistic interaction.

[00310] In Examples 1 to 5, we describe a series of experiments in which a wide variety of representative μ -opioid receptor agonists, accounting for approximately 80 to 90% of dosage units of strong opioids used clinically, were evaluated for their antinociceptive effects in validated non-clinical models of pain. When administered at subanalgesic doses, each of the μ -opioid receptor agonists, morphine, fentanyl, hydromorphone and oxycodone produced minimal antinociception. When co-administered with subanalgesic doses of levorphanol, a putative κ_3 -opioid receptor agonist, morphine, fentanyl, hydromorphone and oxycodone produced a robust and long-lasting analgesic response, demonstrating analgesic synergy. Importantly, the findings of analgesic synergy were confirmed with isobolographic analysis

EXAMPLE 6

[00311] A 47 year-old male patient with an approximately 4-year history of chronic severe unrelieved idiopathic low back pain had previously received

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treatment with a variety of NSAIDs, including ibuprofen, naproxen, meloxicam and valdecoxib; gabapentin; cyclobenzaprine, amitriptyline and TENS with only partial relief. The patient was started on a combination of oral controlled release morphine 15 mg every 12 hours plus oral levorphanol tartrate 2 mg every 8 hours. The patient's pain was well controlled with this combination, without typical opioid side effects, with the exception of constipation, which was treated with a laxative. On a subsequent visit to his primary care physician, the levorphanol was discontinued on the grounds that concurrent use of two opioids was irrational. At this time, the patient's oral controlled release morphine dose was doubled to 30 mg every 12 hours. The patient complained of worsening pain despite approximately two weeks of treatment. The dose of oral controlled release morphine dose was again doubled to 60 mg every 12 hours, with some improvement in pain relief but with the emergence of bothersome side effects. After one week of morphine monotherapy, the patient was reinitiated on oral controlled release morphine 15 mg every 12 hours plus oral levorphanol 2 mg every 8 hours with return of full pain control and without unacceptable side effects.

EXAMPLE 7

A 52 year old female patient with infiltrating ductal carcinoma of the breast and multiple metastasis was treated for her pain with palliative chemo-and radiotherapy, and various opioid, non-opioid and adjuvant analgesics, including NSAIDs, COX-II selective inhibitors and fix dose combinations of 1 to 2 tablets of acetaminophen 325 mg plus oxycodone 5 mg, given as required (i.e., prn). The patient was eventually prescribed transdermal fentanyl 25 µg/hour patch every 3 days. On this dose, the patient had pain relief but continued to have frequent episodes of transitory pain (breakthrough pain) both at rest and with activity. The transdermal fentanyl patch dose was increased at the next application to 50

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µg/hour, but this dose was accompanied by severe drowsiness and fatigue. The dose was dropped back to 25 µg/hour patch every 3 days, and episodes of breakthrough pain were treated with oral transmucosal fentanyl citrate 200 µg every 1-2 hours as required, which provided some relief but the pain relief was often slow in onset (>15 to 20 minutes) and inconsistent. After 4 days, the dose of oral transmucosal fentanyl citrate for breakthrough pain was increased to 400 µg every 1-2 hours as required but the patient continued to experience an average of 5 to 6 episodes of breakthrough pain a day. Oral transmucosal fentanyl citrate was discontinued and breakthrough pain was treated with oral levorphanol tartrate 2 mg every 2-3 hours as required. The patient's episodes of breakthrough pain decreased to 1 to 2 per day and the response to treatment of breakthrough pain episodes was clinically superior (faster onset of effect, more consistent effect, fewer episodes). As the patient's metastatic disease progressed over the next two years, the transdermal fentanyl patch dose was increased to 50 µg/hour every 3 days for maintenance therapy, with levorphanol tartrate 4 mg every 2-3 hours as required for breakthrough pain and eventually to transdermal fentanyl patch dose was increased to 100 µg/hour every 3 days for maintenance therapy, with levorphanol tartrate 6 mg every 2-3 hours as required for breakthrough pain. The patient usually required 1 or 2 doses of oral levorphanol tartrate each day for management of breakthrough pain.

EXAMPLE 8

A 71 year old male patient with radiographically confirmed Grade IV osteoarthritis of the hip and knee and signs and symptoms of chronic pain at rest and with activity, stiffness and crepitus was initially treated with acetaminophen up to 4 grams per day and a variety of NSAIDs. As the patient's pain progressed, he was switched to celecoxib 200 mg daily, with supplemental acetaminophen 1 g as required for exacerbations. He was eventually transferred to controlled release oxycodone 20 mg twice a day. The dose of oral controlled release oxycodone

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was titrated up to 80 mg twice a day over the next three months. Pain was well controlled but the patient suffered from asthenia, fatigue, somnolence and severe constipation (controlled with a stools softener and stimulant laxative). In addition, the patient and his family were concerned about his high opioid requirement. The patient was given a test dose of controlled release oxycodone 20 mg co-administered with oral levorphanol tartrate 2 mg with very good pain relief and without bothersome side effects. The patient was subsequently maintained on a combination of controlled release oxycodone 20 mg twice a day and levorphanol tartrate 2 mg with every 6 hours with an optimal balance between analgesia and side effects. Over approximately the next 18 months, as the patient's knee osteoarthritis worsened, the analgesic dose was increased so that he was receiving a combination of controlled release oxycodone 40 mg twice a day and levorphanol tartrate 4 mg with every 6 to 8 hours with good pain relief.

EXAMPLE 9

A 48 year old male with a prior medical history of acute recurrent episodes of low back pain, exacerbated by vigorous activity, was previously treated with a variety of drugs including NSAIDs (e.g., ibuprofen, naproxen sodium, diclofenac, rofecoxib, celecoxib), fixed-dose opioid and non-opioid combinations (acetaminophen with codeine, acetaminophen with oxycodone, ibuprofen with hydrocodone), tramadol and most recently, with immediate release hydromorphone. Hydromorphone was administered at a dose of 8 to 12 mg every 6 hours, as required. For each episode of acute low back pain, the patient usually took 4 doses of hydromorphone per day for 5 to 14 days. This dose provided complete pain relief, but the relief waned approximately 4 hours after each dose. The patient's wife reported that he was frequently sedated and had nausea at this dose, although a reduction in dose to 4 to 6 mg every 6 hours was inadequate to control his pain. The patient was co-administered a dose of oral hydromorphone 2 mg and oral levorphanol 2 mg every 6 hours with complete pain relief, usually

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lasting for the entire 6 hour dosing interval, with tolerable side effects. The patient was maintained on this dose.

EXAMPLE 10

A 64 year-old female patient with nonresectable non-small cell lung cancer was treated for her pain with NSAIDs, COX-2 selective inhibitors and eventually with fixed combinations of 1 or 2 acetaminophen 325 mg plus oxycodone 5 mg every 6 hours, as required (i.e., prn), with only partial relief. The patient was started on oral controlled release oxycodone 20 mg every 12 hours which was tolerable except for constipation, but with only suboptimal pain relief. The dose of oxycodone was increased to 40 mg every 12 hours with some improvement in pain relief but with the emergence of bothersome nausea and drowsiness. After approximately 4 weeks, the dose of oxycodone was further increased to 80 mg every 12 hours with significant pain relief, but this dose could not be maintained due to severe nausea and drowsiness. A single oral levorphanol tartrate test dose of 2 mg was co-administered with controlled release oxycodone 40 mg, resulting significant pain relief and without bothersome nausea and drowsiness. The controlled release oxycodone maintenance dose was reduced from 80 mg every 12 hours to 40 mg every 12 hours, co-administered with oral levorphanol tartrate 2 mg every eight hours. The patient's pain was well controlled with this combination, without typical opioid side effects, with the exception of constipation, which was treated with a laxative.

EXAMPLE 11

A 67 year old female patient with a long-standing history of knee and hip osteoarthritis was variously treated with ibuprofen, diclofenac, celecoxib and rofecoxib, with reasonably good pain relief. Occasional exacerbations were treated with as needed acetaminophen 1 g up to 3 times per day. With worsening of pain that could not be controlled with non-opioid analgesic plus supplemental acetaminophen, a decision was made to start opioid therapy. The patient was

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initiated on a test dose of the combination of once-daily controlled release morphine 30 mg per day plus levorphanol 2 mg every 8 hours with excellent pain control and only mild nausea, which abated over time. After approximately 4 months of treatment with morphine plus levorphanol, the patient's pain was inadequately controlled on existing doses. Levorphanol was discontinued and the once-daily controlled release morphine dose increased to 60 mg per day without adequate pain control. After two weeks, the dose of once-a-day controlled release morphine was increased to 120 mg a day. This dose provided very good pain control but resulted in significant side effects, including increased sweating, dry mouth, urinary retention, blurred vision, tiredness and "difficulty thinking". The patient was restarted on the combination of once-daily controlled release morphine 30 mg per day plus levorphanol 2 mg every 8 hours, once again with very good pain control and tolerable side effects.

WHAT IS CLAIMED IS:

1. An analgesic composition comprising a subanalgesic dosage of a μ -opioid agonist and a subanalgesic dosage of levorphanol, given together or separately, each in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
2. An analgesic composition comprising an analgesic dosage of a μ -opioid agonist and a subanalgesic dosage of levorphanol, given together or separately, each in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
3. An analgesic composition comprising an analgesic dosage of a μ -opioid agonist and an analgesic dosage of levorphanol, given together or separately, each in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
4. An analgesic composition as claimed in claim 1 to 3 wherein the μ -opioid agonist is selected from oxycodone, morphine, oxymorphone, hydromorphone, hydrocodone, codeine, dihydrocodeine, methadone, meperidine, buprenorphine, tapentadol, fentanyl, carfentanil, lofenatnil, sufentanil, remifentanil.
5. An analgesic composition as claimed in claim 1 to 3 wherein the initial dosages of the μ -opioid agonist and levorphanol have the meaning defined in the specification and are given by the oral, sublingual, buccal, rectal,

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subcutaneous, intravenous, intramuscular, intranasal, inhaled, epidural, spinal, topical, intradermal, intraperitoneal, intracerebroventricular, intra-articular and transdermal routes of administration.

6. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising a subanalgesic dosage of a μ -opioid agonist and a subanalgesic dosage of levorphanol each given in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
7. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid agonist and a subanalgesic dosage of levorphanol each given in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
8. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid agonist and an analgesic dosage of levorphanol each given in the form of a base or, optionally, in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
9. A method as claimed in claim 6 to 8 wherein the μ -opioid agonist is selected from oxycodone, morphine, oxymorphone, hydromorphone,

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hydrocodone, codeine, dihydrocodeine, methadone, meperidine, buprenorphine, tapentadol, fentanyl, carfentanil, lofenatnil, sufentanil, remifentanil.

10. A method as claimed in claim 6 to 8 wherein the initial dosages of the μ -opioid agonist and levorphanol have the meaning defined in the specification and are given by the oral, sublingual, buccal, rectal, subcutaneous, intravenous, intramuscular, intranasal, inhaled, epidural, spinal, topical, intradermal, intraperitoneal, intracerebroventricular, intra-articular and transdermal routes of administration.
11. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered in a single dosage form.
12. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered in separate dosage forms.
13. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered by the same route of administration.
14. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered by different routes of administration.
15. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered at about the same time.
16. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of the μ -opioid agonist and the dosage of levorphanol are administered at different times.
17. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of levorphanol is administered

intermittently to subjects receiving around the clock or regularly scheduled μ -opioid agonists.

18. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage of levorphanol is administered intermittently to subjects receiving μ -opioid agonists on an as required basis.
19. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage range of the μ -opioid agonist and levorphanol defined in the specification are mass units of base.
20. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, wherein the dosage range of the μ -opioid agonist and levorphanol defined in the specification are mass units of pharmaceutical acceptable salt.
21. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, directed to novel pharmaceutical compositions of matter and methods for enhancing the analgesic effect of the μ -opioid receptor agonist.
22. A composition as claimed in claims 1 to 3 and a method as claimed in claims 6 to 8, directed to novel pharmaceutical compositions of matter and methods for reducing undesirable opioid side effects.
23. An analgesic composition wherein the dosage of levorphanol is administered intermittently as required for the treatment of pain, including breakthrough pain, in subjects receiving μ -opioid agonists.
24. An method of treating pain, wherein the dosage of levorphanol is administered intermittently as required for the treatment of pain, including breakthrough pain, in subjects receiving μ -opioid agonists.
25. An analgesic composition comprising a subanalgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect, expressed in morphine

analgesic equivalents, is selected from the group consisting of:

- (A) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 6.25 mg;
- (B) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 5 mg;
- (C) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 3.75 mg;
- (D) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 2.5 mg;
- (E) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 1.875 mg;
- (F) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.875 mg;
- (G) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.25 mg;
- (H) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.875 mg;
- (I) An initial dosage of for a naïve human adult through an epidural route between about 0.01 mg and about 0.5 mg;
- (J) An initial dosage for a naïve human adult through an epidural route between about 0.01 mg and about 0.25 mg;

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- (K) An initial dosage for a naive human adult through an epidural route between about 0.01 mg and about 0.125 mg;
- (L) An initial dosage for a naive human adult through the spinal route is between about 0.001 mg and about 0.004 mg;
- (M) An initial dosage for a naive human adult through the spinal route is between about 0.001 mg and about 0.002 mg;
- (N) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.025 mg/kg and about 0.1mg/kg;
- (O) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.025 mg/kg and about 0.05mg/kg;
- (P) An initial dosage for a naive human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.0025 mg/kg and about 0.01 mg/kg;
- (Q) an initial dosage for a naive lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

OR

An analgesic composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- (a) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 6.25 mg and about 30 mg;
- (b) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 5 mg and about 30 mg;
- (c) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 3.75 mg and about 30 mg;

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- (d) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 2.5 mg and about 30 mg;
- (e) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 1.875 mg and about 30 mg;
- (f) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.875 mg and about 15 mg;
- (g) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 15 mg;
- (h) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.875 mg and about 15 mg;
- (i) An initial dosage of for a human adult through an epidural route between about 0.5 mg and about 5 mg;
- (j) An initial dosage for a human adult through an epidural route between about 0.25 mg and about 5 mg;
- (k) An initial dosage for a human adult through an epidural route between about 0.125 mg and about 5 mg;
- (l) An initial dosage for a human adult through the spinal route is between about 0.004 mg and about 0.5 mg;
- (m) An initial dosage for a human adult through the spinal route is between about 0.002 mg and about 0.5 mg;
- (n) An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.5 mg;
- (o) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.1 mg/kg and about 1 mg/kg;

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- (p) An initial dosage for a naïve human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.05 mg/kg and about 1 mg/kg;
- (q) An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.01 mg/kg and about 0.5 mg/kg;
- (r) an initial dosage for a lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

AND

a subanalgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect is selected from the group consisting of:

- (I) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.666 mg;
- (II) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.5 mg;
- (III) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.333 mg;
- (IV) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route, is between about 0.01875 mg and about 0.166 mg;
- (V) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.025 mg and about 0.333 mg;
- (VI) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled

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route between about 0.025 mg and about 0.166 mg;

- (VII) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.025 mg and about 0.0833 mg;
- (VIII) An initial dosage of for a naïve human adult through an epidural route between about 0.002 mg and about 0.1 mg;
- (IX) An initial dosage for a naïve human adult through an epidural route between about 0.002 mg and about 0.075 mg;
- (X) An initial dosage for a naïve human adult through an epidural route between about 0.002 mg and about 0.05 mg;
- (XI) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.001 mg;
- (XII) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.0005 mg;
- (XIII) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.00025 mg;
- (XIV) An initial dosage for a naïve human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.00025 mg/kg and about 0.01 mg/kg;
- (XV) An initial dosage for a naïve human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.00025 mg/kg and about 0.005 mg/kg;
- (XVI) An initial dosage for a naïve human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.000125 mg/kg and about 0.005 mg/kg;
- (XVII) an initial subanalgesic dosage for a naïve lower animal through an oral or parenteral route is between about 0.025 mg/kg and about 0.5 mg/kg.

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OR

a dosage of levorphanol or its pharmaceutically acceptable salt for the treatment of breakthrough pain, selected from the group consisting of:

1. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 4 mg per rescue dose, as required;
2. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 3 mg per rescue dose, as required;
3. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 2 mg per rescue dose, as required;
4. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 1 mg per rescue dose, as required;
5. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 0.5 mg per rescue dose, as required;
6. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 2 mg per rescue dose, as required;
7. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.5 mg per rescue dose, as required;
8. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1 mg per rescue dose,

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as required;

9. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.5 mg per rescue dose, as required;
10. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.25 mg per rescue dose, as required;
11. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 4 mg and about 36 mg per rescue dose, as required;
12. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 3 mg and about 36 mg per rescue dose, as required;
13. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 2 mg and about 36 mg per rescue dose, as required;
14. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 1 mg and about 36 mg per rescue dose, as required;
15. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 36 mg per rescue dose, as required;
16. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 2 mg and about 18 mg per rescue dose, as required;
17. An initial dosage for a human adult administered through a

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- subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.5 mg and about 18 mg per rescue dose, as required;
18. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1 mg and about 18 mg per rescue dose, as required;
19. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.5 mg and about 18 mg per rescue dose, as required;
20. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.25 mg and about 18 mg per rescue dose, as required.
26. An analgesic composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect, expressed in morphine analgesic equivalents, is selected from the group consisting of:
- (A) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 6.25 mg and about 30 mg;
 - (B) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 5 mg and about 30 mg;
 - (C) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 3.75 mg and about 30 mg;
 - (D) An initial dosage for a human adult through an oral, rectal,

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buccal, transmucosal or sublingual route between about 2.5 mg and about 30 mg;

- (E) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 1.875 mg and about 30 mg;
- (F) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.875 mg and about 15 mg;
- (G) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 15 mg;
- (H) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.875 mg and about 15 mg;
- (I) An initial dosage of for a human adult through an epidural route between about 0.5 mg and about 5 mg;
- (J) An initial dosage for a human adult through an epidural route between about 0.25 mg and about 5 mg;
- (K) An initial dosage for a human adult through an epidural route between about 0.125 mg and about 5 mg;
- (L) An initial dosage for a human adult through the spinal route is between about 0.004 mg and about 0.5 mg;
- (M) An initial dosage for a human adult through the spinal route is between about 0.002 mg and about 0.5 mg;
- (N) An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.5 mg;
- (O) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.1 mg/kg and about 1 mg/kg;

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- (P) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.05 mg/kg and about 1 mg/kg;
- (Q) An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.01 mg/kg and about 0.5 mg/kg;
- (R) an initial dosage for a lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

AND

An analgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect is selected from the group consisting of:

- (I) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.666 mg and about 6 mg;
- (II) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 6 mg;
- (III) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.333 mg and about 6 mg;
- (IV) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route, is between about 0.166 mg and about 6 mg;
- (V) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.333 mg and about 2 mg;
- (VI) An initial dosage for a human adult through a

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subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.166 mg and about 2 mg;

(VII) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.0833 mg and about 2 mg;

(VIII) An initial dosage of for a human adult through an epidural route between about 0.1 mg and about 2 mg;

(IX) An initial dosage for a human adult through an epidural route between about 0.075 mg and about 2 mg;

(X) An initial dosage for a human adult through an epidural route between about 0.05 mg and about 2 mg;

(XI) An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.1 mg;

(XII) An initial dosage for a human adult through the spinal route is between about 0.0005 mg and about 0.1 mg;

(XIII) An initial dosage for a human adult through the spinal route is between about 0.00025 mg and about 0.1 mg;

(XIV) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01 mg/kg and about 0.2 mg/kg;

(XV) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.005 mg/kg and about 0.2 mg/kg;

(XVI) An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.005 mg/kg and about 0.1 mg/kg;

(XVII) an initial subanalgesic dosage for a lower animal through an oral or parenteral route is between about 0.5 mg/kg and about 5 mg/kg.

OR

a dosage of levorphanol or its pharmaceutically acceptable salt for the treatment of breakthrough pain, selected from the group consisting of:

1. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 4 mg per rescue dose, as required;
2. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 3 mg per rescue dose, as required;
3. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 2 mg per rescue dose, as required;
4. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 1 mg per rescue dose, as required;
5. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 0.5 mg per rescue dose, as required;
6. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 2 mg per rescue dose, as required;
7. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.5 mg per rescue dose, as required;
8. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1 mg per rescue dose, as required;
9. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about

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- 0.125 mg and about 0.5 mg per rescue dose, as required;
10. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.25 mg per rescue dose, as required;
 11. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 4 mg and about 36 mg per rescue dose, as required;
 12. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 3 mg and about 36 mg per rescue dose, as required;
 13. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 2 mg and about 36 mg per rescue dose, as required;
 14. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 1 mg and about 36 mg per rescue dose, as required;
 15. An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 36 mg per rescue dose, as required;
 16. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 2 mg and about 18 mg per rescue dose, as required;
 17. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.5 mg and about 18 mg per rescue dose, as required;
 18. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1 mg and about 18 mg per rescue dose, as required;
 19. An initial dosage for a human adult administered through a subcutaneous,

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- intravenous, intramuscular, intranasal or inhaled route between about 0.5 mg and about 18 mg per rescue dose, as required;
20. An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.25 mg and about 18 mg per rescue dose, as required.
27. A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such treatment a composition comprising a subanalgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, for each hour of the intended duration of effect, expressed in morphine analgesic equivalents, is selected from the group consisting of:
- (A) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 6.25 mg;
 - (B) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 5 mg;
 - (C) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 3.75 mg;
 - (D) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 2.5 mg;
 - (E) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 1.875 mg;
 - (F) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.875 mg;

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- (G) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.25 mg;
- (H) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.875 mg;
- (I) An initial dosage of for a naïve human adult through an epidural route between about 0.01 mg and about 0.5 mg;
- (J) An initial dosage for a naïve human adult through an epidural route between about 0.01 mg and about 0.25 mg;
- (K) An initial dosage for a naïve human adult through an epidural route between about 0.01 mg and about 0.125 mg;
- (L) An initial dosage for a naïve human adult through the spinal route is between about 0.001 mg and about 0.004 mg;
- (M) An initial dosage for a naïve human adult through the spinal route is between about 0.001 mg and about 0.002 mg;
- (N) An initial dosage for a naïve human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.025 mg/kg and about 0.1mg/kg;
- (O) An initial dosage for a naïve human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.025 mg/kg and about 0.05mg/kg;
- (P) An initial dosage for a naïve human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.0025 mg/kg and about 0.01 mg/kg;
- (Q) an initial dosage for a naïve lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

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OR

A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, for each hour of the intended duration of effect, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- (a) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 6.25 mg and about 30 mg;
- (b) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 5 mg and about 30 mg;
- (c) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 3.75 mg and about 30 mg;
- (d) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 2.5 mg and about 30 mg;
- (e) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 1.875 mg and about 30 mg;
- (f) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.875 mg and about 15 mg;
- (g) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 15 mg;
- (h) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.875 mg and about 15 mg;
- (i) An initial dosage of for a human adult through an epidural route between about 0.5 mg and about 5 mg;

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- (j) An initial dosage for a human adult through an epidural route between about 0.25 mg and about 5 mg;
- (k) An initial dosage for a human adult through an epidural route between about 0.125 mg and about 5 mg;
- (l) An initial dosage for a human adult through the spinal route is between about 0.004 mg and about 0.5 mg;
- (m) An initial dosage for a human adult through the spinal route is between about 0.002 mg and about 0.5 mg;
- (n) An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.5 mg;
- (o) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.1 mg/kg and about 1 mg/kg;
- (p) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.05 mg/kg and about 1 mg/kg;
- (q) An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.01 mg/kg and about 0.5 mg/kg;
- (r) an initial dosage for a lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

AND

a subanalgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect is selected from the group consisting of:

- (I) An initial dosage for a naive human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.666 mg;
- (II) An initial dosage for a naive human adult through an oral, rectal,

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buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.5 mg;

(III) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01875 mg and about 0.333 mg;

(IV) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route, is between about 0.01875 mg and about 0.166 mg;

(V) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.025 mg and about 0.333 mg;

(VI) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.025 mg and about 0.166 mg;

(VII) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.025 mg and about 0.0833 mg;

(VIII) An initial dosage of for a naïve human adult through an epidural route between about 0.002 mg and about 0.1 mg;

(IX) An initial dosage for a naïve human adult through an epidural route between about 0.002 mg and about 0.075 mg;

(X) An initial dosage for a naïve human adult through an epidural route between about 0.002 mg and about 0.05 mg;

(XI) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.001 mg;

(XII) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.0005 mg;

(XIII) An initial dosage for a naïve human adult through the spinal route is between about 0.00005 mg and about 0.00025 mg;

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- (XIV) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.00025 mg/kg and about 0.01 mg/kg;
- (XV) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.00025 mg/kg and about 0.005 mg/kg;
- (XVI) An initial dosage for a naive human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.000125 mg/kg and about 0.005 mg/kg;
- (XVII) an initial subanalgesic dosage for a naive lower animal through an oral or parenteral route is between about 0.025 mg/kg and about 0.5 mg/kg;

OR

a dosage of levorphanol or its pharmaceutically acceptable salt for the treatment of breakthrough pain, selected from the group consisting of:

- 1) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 4 mg per rescue dose, as required;
- 2) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 3 mg per rescue dose, as required;
- 3) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 2 mg per rescue dose, as required;
- 4) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 1 mg per rescue dose, as required;
- 5) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between

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- about 0.25 mg and about 0.5 mg per rescue dose, as required;
- 6) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 2 mg per rescue dose, as required;
 - 7) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.5 mg per rescue dose, as required;
 - 8) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1 mg per rescue dose, as required;
 - 9) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.5 mg per rescue dose, as required;
 - 10) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.25 mg per rescue dose, as required;
 - 11) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 4 mg and about 36 mg per rescue dose, as required;
 - 12) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 3 mg and about 36 mg per rescue dose, as required;
 - 13) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between

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about 2 mg and about 36 mg per rescue dose, as required;

- 14) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 1 mg and about 36 mg per rescue dose, as required;
- 15) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 36 mg per rescue dose, as required;
- 16) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 2 mg and about 18 mg per rescue dose, as required;
- 17) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.5 mg and about 18 mg per rescue dose, as required;
- 18) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1 mg and about 18 mg per rescue dose, as required;
- 19) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.5 mg and about 18 mg per rescue dose, as required;
- 20) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.25 mg and about 18 mg per rescue dose, as required.

28. A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such

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treatment a composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, for each hour of the intended duration of effect, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- (A) An initial dosage for a naïve human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 6.25 mg and about 30 mg;
- (B) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 5 mg and about 30 mg;
- (C) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 3.75 mg and about 30 mg;
- (D) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 2.5 mg and about 30 mg;
- (E) An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 1.875 mg and about 30 mg;
- (F) An initial dosage for a naïve human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.875 mg and about 15 mg;
- (G) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 15 mg;
- (H) An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.875 mg and about 15 mg;
- (I) An initial dosage of for a human adult through an epidural

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route between about 0.5 mg and about 5 mg;

(J) An initial dosage for a human adult through an epidural route between about 0.25 mg and about 5 mg;

(K) An initial dosage for a human adult through an epidural route between about 0.125 mg and about 5 mg;

(L) An initial dosage for a human adult through the spinal route is between about 0.004 mg and about 0.5 mg;

(M) An initial dosage for a human adult through the spinal route is between about 0.002 mg and about 0.5 mg;

(N) An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.5 mg;

(O) An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.1 mg/kg and about 1 mg/kg;

(P) An initial dosage for a naive human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.05 mg/kg and about 1 mg/kg;

(Q) An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.01 mg/kg and about 0.5 mg/kg;

(R) an initial dosage for a lower animal through an oral or parenteral route is between about 0.01 mg/kg and about 1.25 mg/kg.

AND

An analgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage for each hour of the intended duration of effect is selected from the group consisting of:

- I. An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.666 mg and about

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6 mg;

- II. An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 6 mg;
- III. An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route between about 0.333 mg and about 6 mg;
- IV. An initial dosage for a human adult through an oral, rectal, buccal, transmucosal or sublingual route, is between about 0.166 mg and about 6 mg;
- V. An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.333 mg and about 2 mg;
- VI. An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.166 mg and about 2 mg;
- VII. An initial dosage for a human adult through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.0833 mg and about 2 mg;
- VIII. An initial dosage of for a human adult through an epidural route between about 0.1 mg and about 2 mg;
- IX. An initial dosage for a human adult through an epidural route between about 0.075 mg and about 2 mg;
- X. An initial dosage for a human adult through an epidural route between about 0.05 mg and about 2 mg;
- XI. An initial dosage for a human adult through the spinal route is between about 0.001 mg and about 0.1 mg;
- XII. An initial dosage for a human adult through the spinal route is between about 0.0005 mg and about 0.1 mg;

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- XIII. An initial dosage for a human adult through the spinal route is between about 0.00025 mg and about 0.1 mg;
- XIV. An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.01 mg/kg and about 0.2 mg/kg;
- XV. An initial dosage for a human child through an oral, rectal, buccal, transmucosal or sublingual route between about 0.005 mg/kg and about 0.2 mg/kg;
- XVI. An initial dosage for a human child through the subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.005 mg/kg and about 0.1 mg/kg;
- XVII. an initial subanalgesic dosage for a lower animal through an oral or parenteral route is between about 0.5 mg/kg and about 5 mg/kg;

OR

a dosage of levorphanol or its pharmaceutically acceptable salt for the treatment of breakthrough pain, selected from the group consisting of:

- 1) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 4 mg per rescue dose, as required;
- 2) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 3 mg per rescue dose, as required;
- 3) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 2 mg per rescue dose, as required;
- 4) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.25 mg and about 1 mg per rescue dose, as required;
- 5) An initial dosage for a human adult administered through an oral, rectal,

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- buccal, transmucosal or sublingual route between about 0.25 mg and about 0.5 mg per rescue dose, as required;
- 6) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 2 mg per rescue dose, as required;
 - 7) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1.5 mg per rescue dose, as required;
 - 8) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 1 mg per rescue dose, as required;
 - 9) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.5 mg per rescue dose, as required;
 - 10) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.125 mg and about 0.25 mg per rescue dose, as required;
 - 11) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 4 mg and about 36 mg per rescue dose, as required;
 - 12) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 3 mg and about 36 mg per rescue dose, as required;
 - 13) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 2 mg and about 36 mg per rescue dose, as required;
 - 14) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 1 mg and about 36 mg per rescue dose, as required;

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- 15) An initial dosage for a human adult administered through an oral, rectal, buccal, transmucosal or sublingual route between about 0.5 mg and about 36 mg per rescue dose, as required;
- 16) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 2 mg and about 18 mg per rescue dose, as required;
- 17) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1.5 mg and about 18 mg per rescue dose, as required;
- 18) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 1 mg and about 18 mg per rescue dose, as required;
- 19) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.5 mg and about 18 mg per rescue dose, as required;
- 20) An initial dosage for a human adult administered through a subcutaneous, intravenous, intramuscular, intranasal or inhaled route between about 0.25 mg and about 18 mg per rescue dose, as required.
29. An analgesic composition comprising a subanalgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:
 - (A) An initial dosage for a naïve human adult through intravenous patient controlled analgesia between about 0.1 mg and about 0.75 mg every 3 to 10 minutes;
 - (B) An initial dosage for a naïve human adult through intravenous patient controlled analgesia between about 0.1 mg and about 0.5 mg every 3 to 10 minutes;
 - (C) An initial dosage for a naïve human adult through intravenous

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patient controlled analgesia between about 0.1 mg and about 0.35 mg every 3 to 10 minutes;

(D) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg/hr and about 1.875 mg/hr;

(E) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg mg/hr and about 1.25 mg/hr;

(F) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg/hr and about 0.875 mg/hr.

OR

An analgesic composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- A. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.75 mg and about 6 mg every 3 to 10 minutes;
- B. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.5 mg and about 6 mg every 3 to 10 minutes;
- C. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.35 mg and about 6 mg every 3 to 10 minutes;
- D. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.875 mg/hr and about 4 mg/hr;
- E. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.25 mg mg/hr and about 4 mg/hr;
- F. An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.875 mg/hr and about 4 mg/hr.

AND

a subanalgesic dosage of levorphanol or its pharmaceutically acceptable salt,

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wherein the dosage is selected from the group consisting of:

- (I) An initial dosage of levorphanol for a naïve human adult through intravenous patient controlled analgesia between about 0.05 mg and about 0.25 mg every 3 to 20 minutes;
- (II) An initial dosage for a naïve human adult through intravenous patient controlled analgesia is between about 0.25 mg and about 0.15 mg every 3 to 20 minutes;
- (III) An initial dosage for a naïve human adult through intravenous patient controlled analgesia is between about 0.05 mg and about 0.1 mg every 3 to 20 minutes.

30. An analgesic composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- G. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.75 mg and about 6 mg every 3 to 10 minutes;
- H. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.5 mg and about 6 mg every 3 to 10 minutes;
- I. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.35 mg and about 6 mg every 3 to 10 minutes;
- J. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.875 mg/hr and about 4 mg/hr;
- K. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.25 mg mg/hr and about 4 mg/hr;
- L. An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.875 mg/hr and about 4 mg/hr.

AND

An analgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage is selected from the group consisting of:

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- (I) An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.25 mg and about 3 mg every 3 to 20 minutes;
- (II) An initial dosage for a human adult through intravenous patient controlled analgesia is between about 0.15 mg and about 3 mg every 3 to 20 minutes;
- (III) An initial dosage for a human adult through intravenous patient controlled analgesia is between about 0.01 mg and about 3 mg every 3 to 20 minutes.

31. A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such treatment a composition comprising a subanalgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- (A) An initial dosage for a naïve human adult through intravenous patient controlled analgesia between about 0.1 mg and about 0.75 mg every 3 to 10 minutes;
- (B) An initial dosage for a naïve human adult through intravenous patient controlled analgesia between about 0.1 mg and about 0.5 mg every 3 to 10 minutes;
- (C) An initial dosage for a naïve human adult through intravenous patient controlled analgesia between about 0.1 mg and about 0.35 mg every 3 to 10 minutes;
- (D) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg/hr and about 1.875 mg/hr;
- (E) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg mg/hr and about

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1.25 mg/hr;

- (F) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.125 mg/hr and about 0.875 mg/hr.

OR

A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- (a) An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.75 mg and about 6 mg every 3 to 10 minutes;
- (b) An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.5 mg and about 6 mg every 3 to 10 minutes;
- (c) An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.35 mg and about 6 mg every 3 to 10 minutes;
- (d) An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.875 mg/hr and about 4 mg/hr;
- (e) An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.25 mg mg/hr and about 4 mg/hr;
- (f) An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.875 mg/hr and about 4 mg/hr.

AND

a subanalgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage is selected from the group consisting of:

- (I) An initial dosage of levorphanol for a naïve human adult through intravenous patient controlled analgesia between about 0.05 mg and about 0.25 mg every 3 to 20 minutes;
- (II) An initial dosage for a naïve human adult through intravenous

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patient controlled analgesia is between about 0.25 mg and about 0.15 mg every 3 to 20 minutes;

(III) An initial dosage for a naïve human adult through intravenous patient controlled analgesia is between about 0.05 mg and about 0.1 mg every 3 to 20 minutes.

32. A method for producing analgesia in humans and lower animals which comprises administering to a human or lower animal in need of such treatment a composition comprising an analgesic dosage of a μ -opioid agonist or its pharmaceutically acceptable salt, wherein the dosage, expressed in morphine analgesic equivalents, is selected from the group consisting of:

- A. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.75 mg and about 6 mg every 3 to 10 minutes;
- B. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.5 mg and about 6 mg every 3 to 10 minutes;
- C. An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.35 mg and about 6 mg every 3 to 10 minutes;
- D. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.875 mg/hr and about 4 mg/hr;
- E. An initial dosage for a naïve human adult through continuous intravenous infusion between about 1.25 mg mg/hr and about 4 mg/hr;
- F. An initial dosage for a naïve human adult through continuous intravenous infusion between about 0.875 mg/hr and about 4 mg/hr.

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AND

An analgesic dosage of levorphanol or its pharmaceutically acceptable salt, wherein the dosage is selected from the group consisting of:

- (I) An initial dosage for a human adult through intravenous patient controlled analgesia between about 0.25 mg and about 3 mg every 3 to 20 minutes;
- (II) An initial dosage for a human adult through intravenous patient controlled analgesia is between about 0.15 mg and about 3 mg every 3 to 20 minutes;
- (III) An initial dosage for a human adult through intravenous patient controlled analgesia is between about 0.01 mg and about 3 mg every 3 to 20 minutes.

Figure 1 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 30 Minutes (Tail-flick Test)

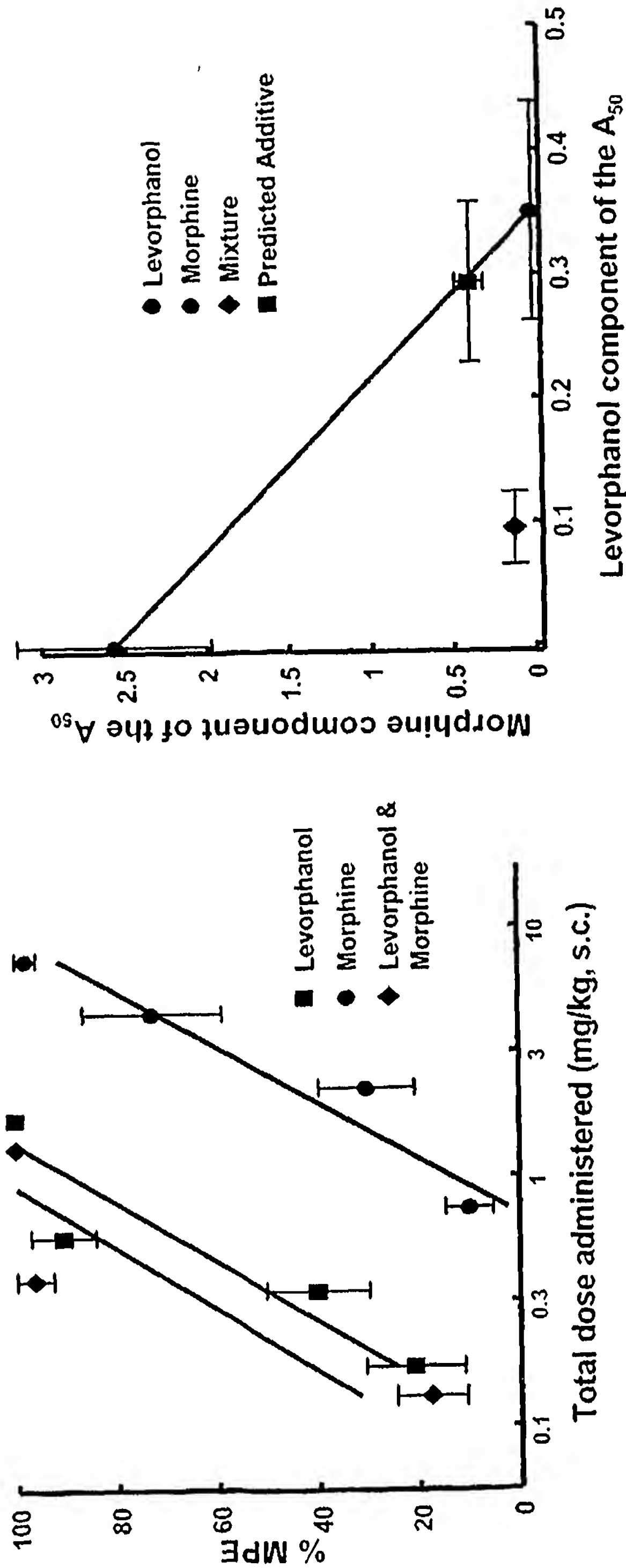


Figure 2 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 45 Minutes (Tail-flick Test)

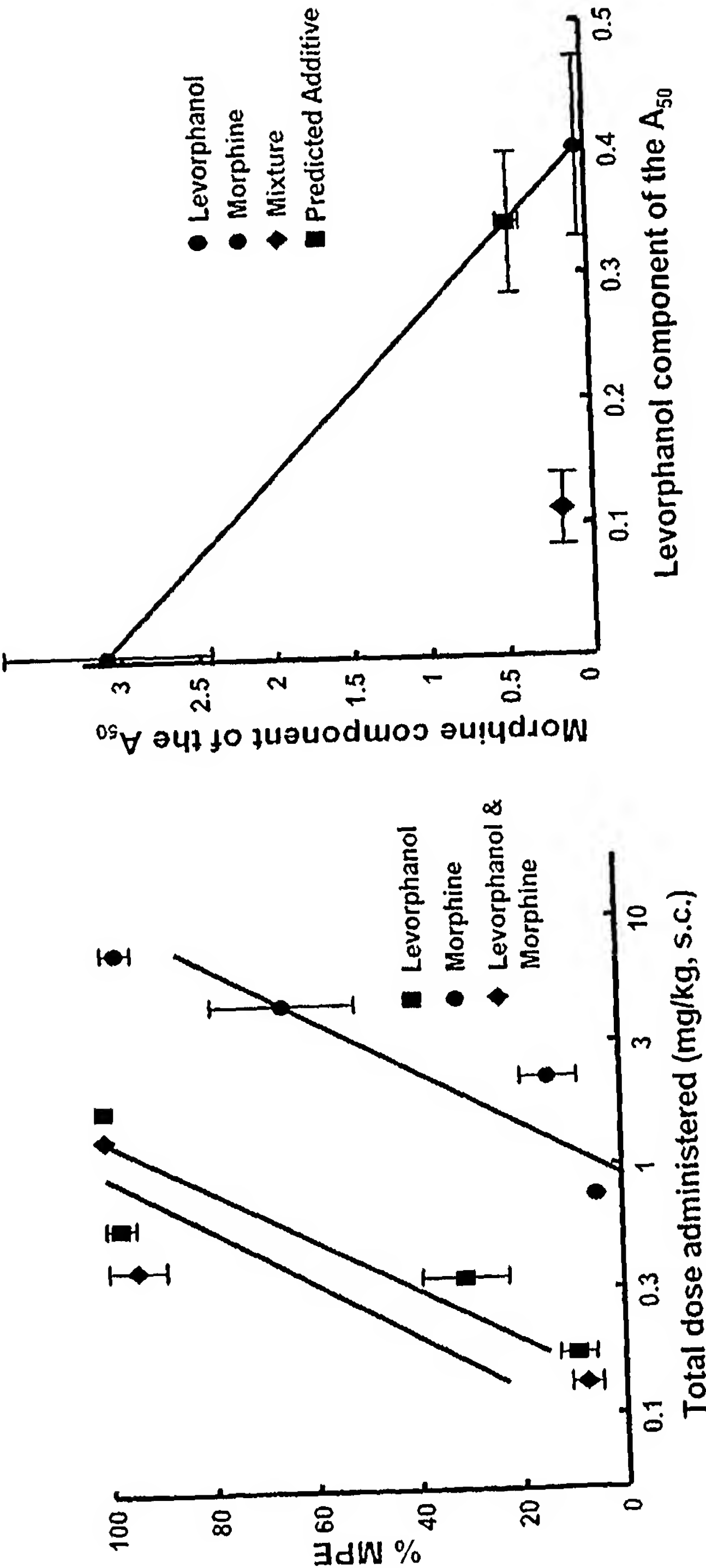


Figure 3 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 60 Minutes (Tail-flick Test)

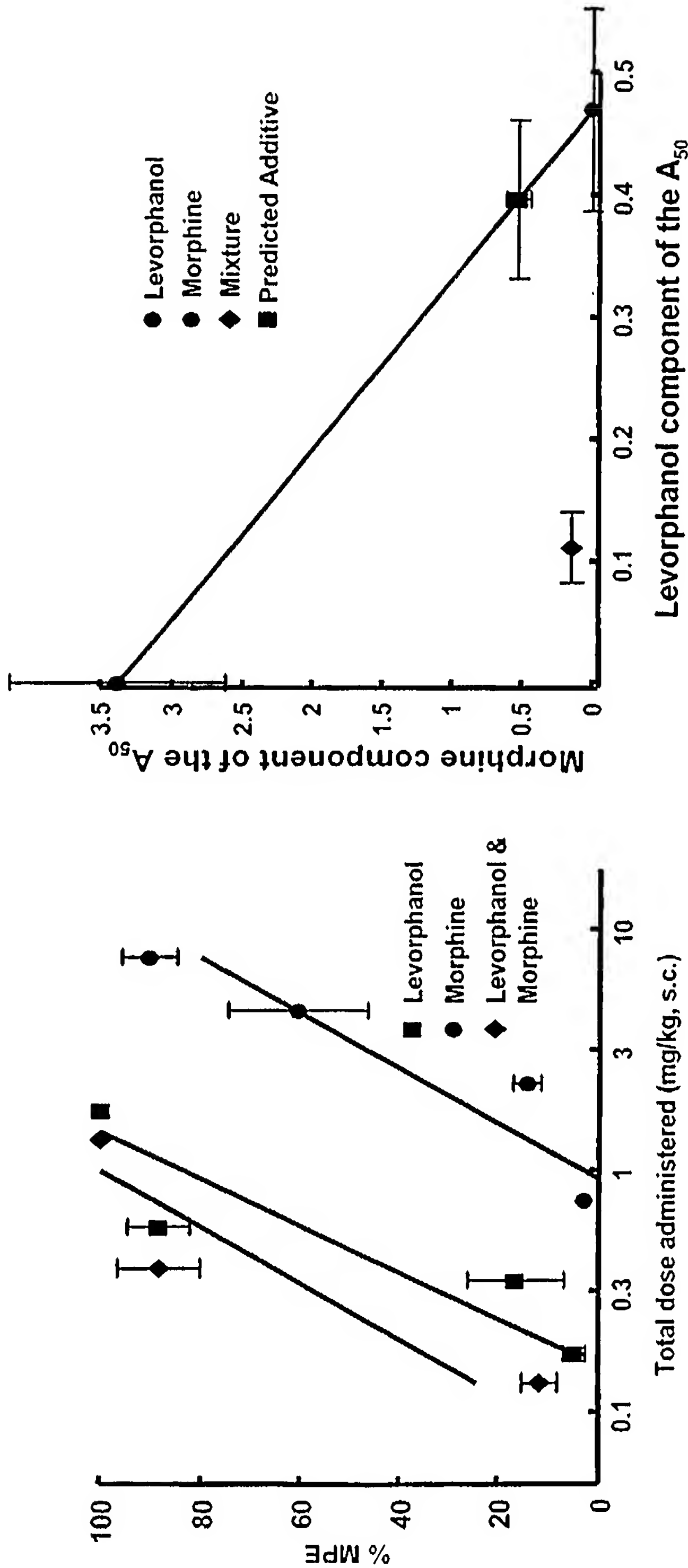


Figure 4 of 25: Antinociceptive Dose-Response Curve for Levorphanol and Morphine at 90 Minutes (Tail-flick Test)

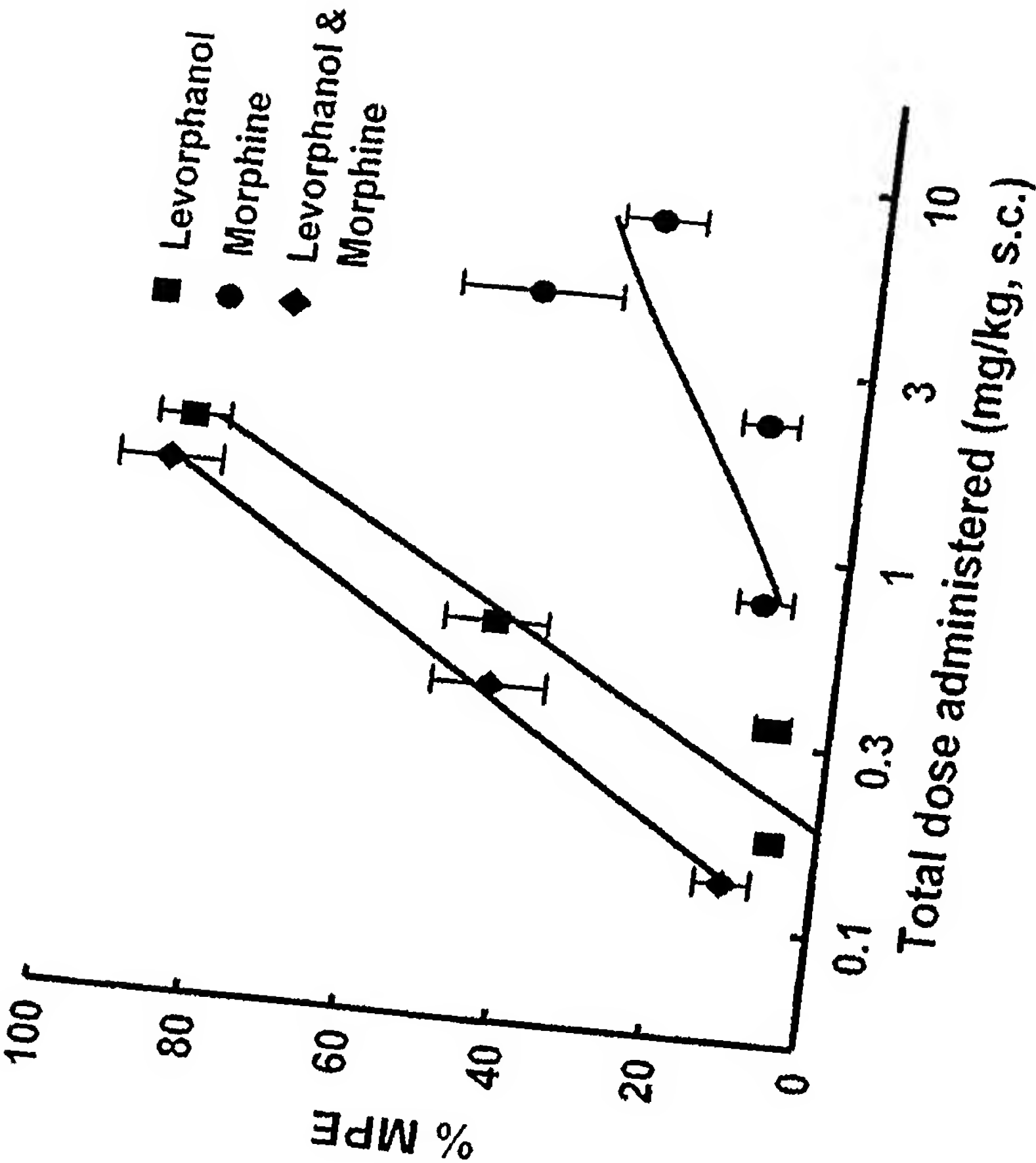


Figure 5 of 25: Antinociceptive Dose-Response Curve for Levorphanol and Morphine at 120 Minutes (Tail-flick Test)

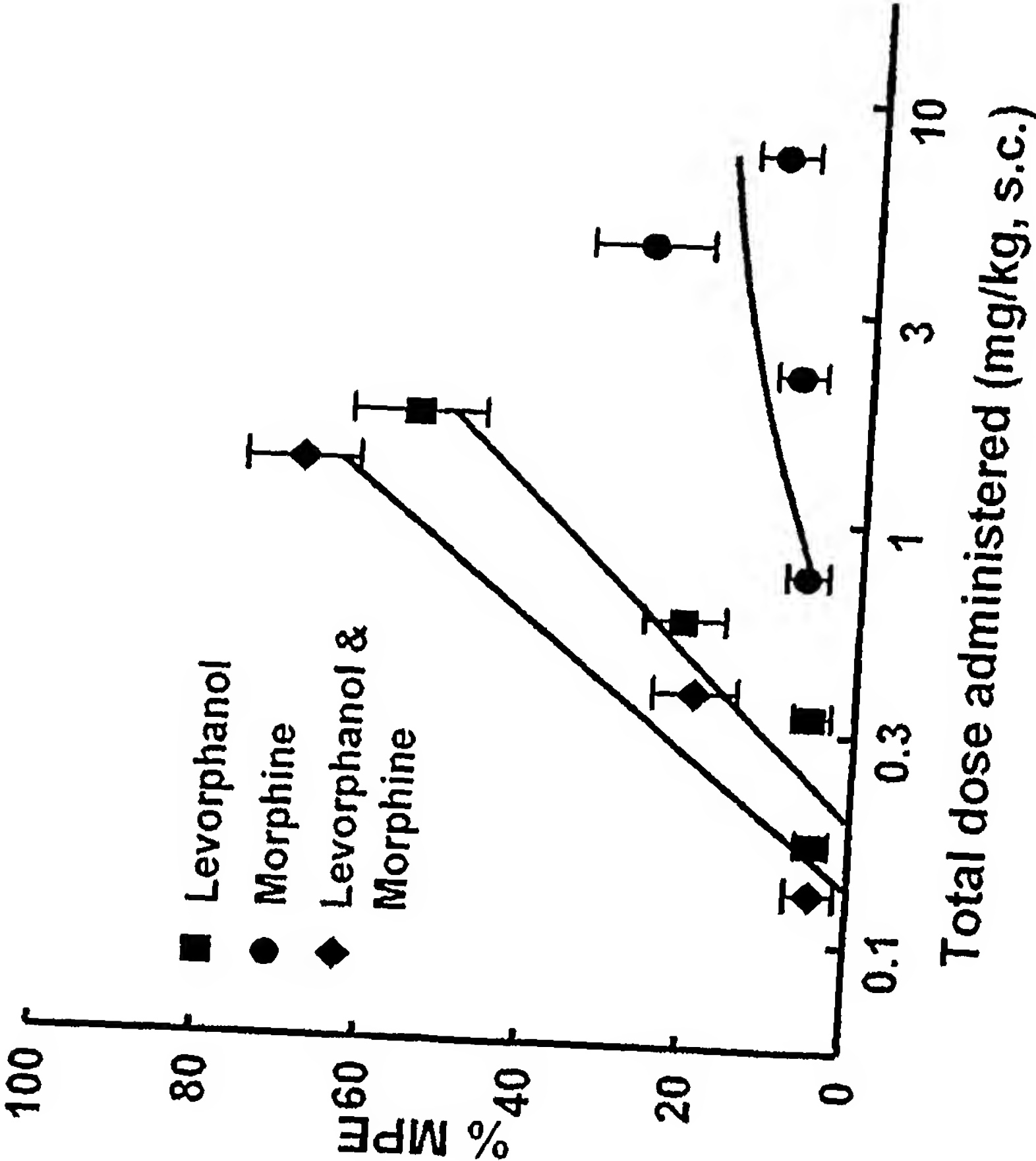


Figure 6 of 25: Antinociceptive Time-course of Low Doses of Levorphanol and Morphine (Tail-flick Test)

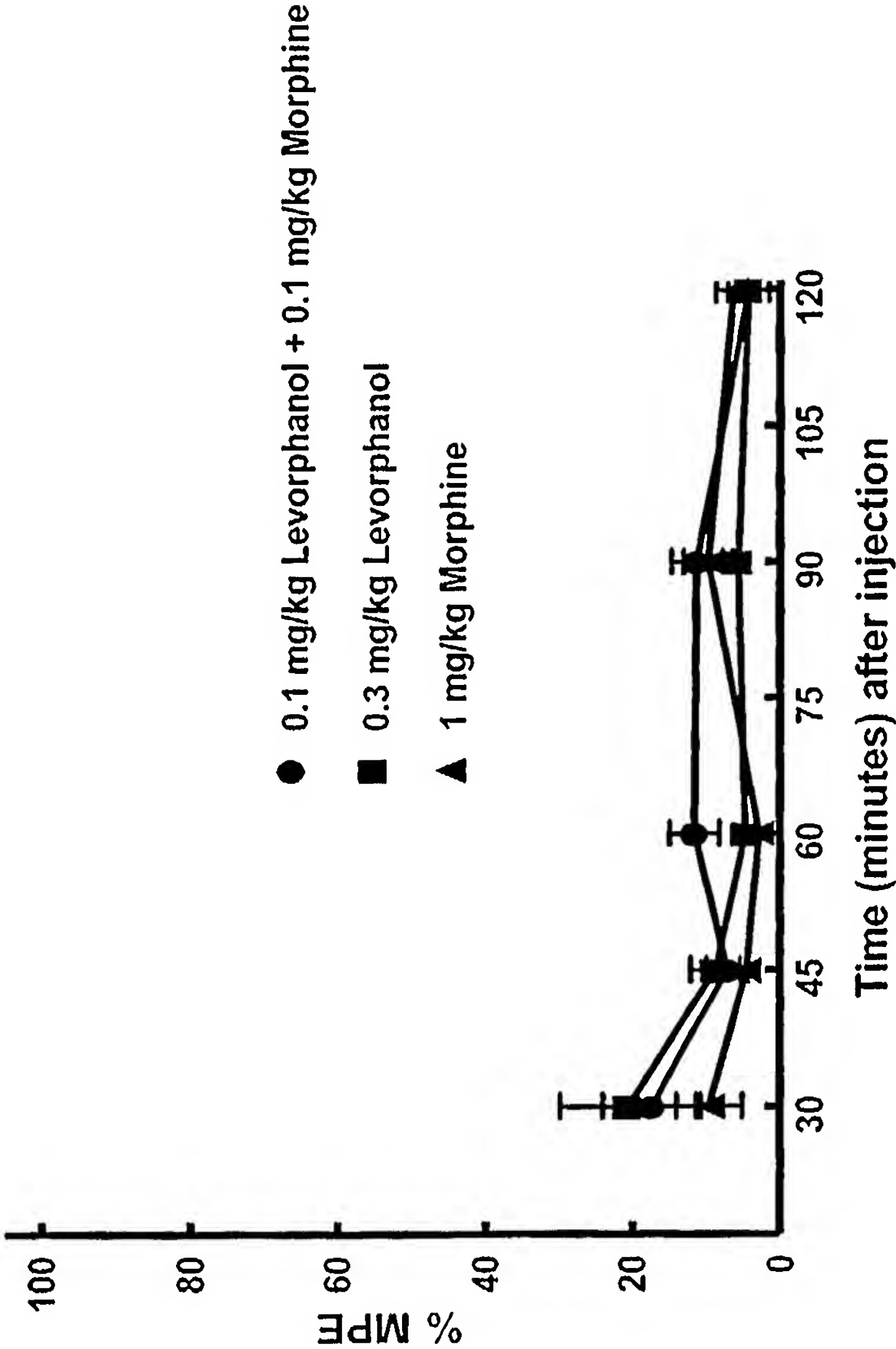


Figure 7 of 25: Antinociceptive Time-course of Intermediate Doses of Levorphanol and Morphine (Tail-flick Test)

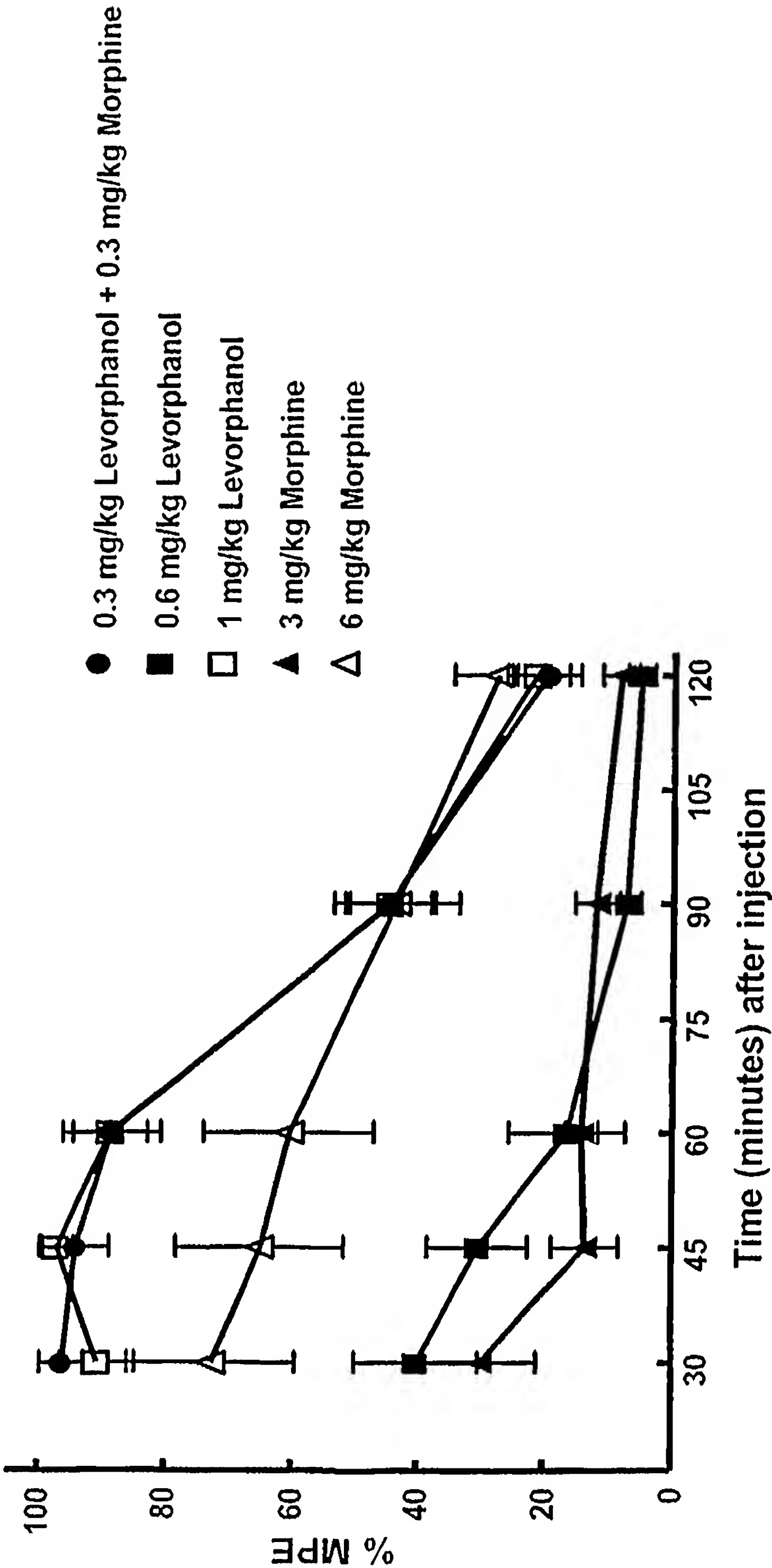


Figure 8 of 25: Antinociceptive Time-course of High Doses of Levorphanol and Morphine (Tail-flick Test)

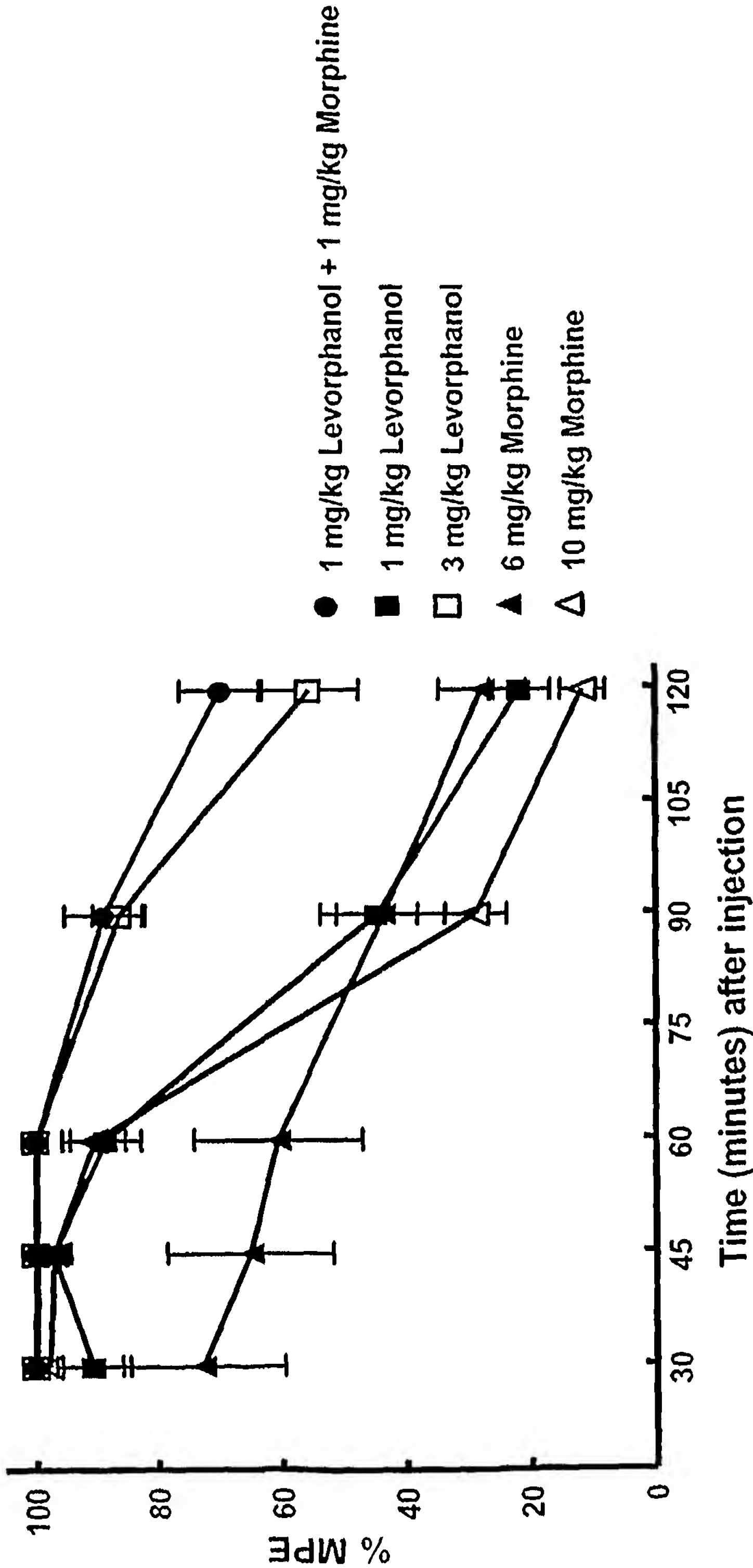


Figure 9 of 25: Antinociceptive Time-course of Morphine (Tail-flick Test)

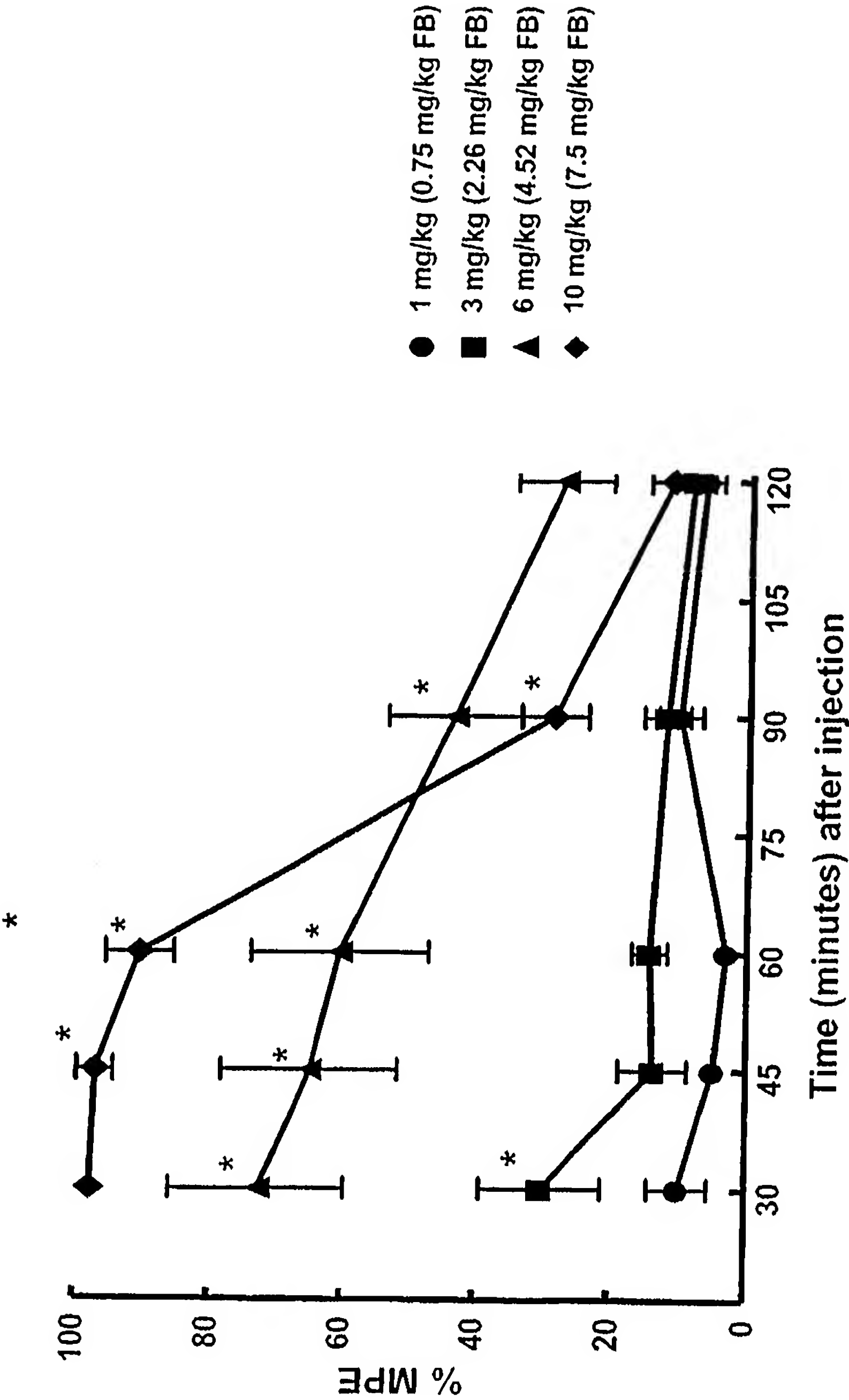


Figure 10 of 25: Antinociceptive Time-course of Levorphanol (Tail-flick Test)

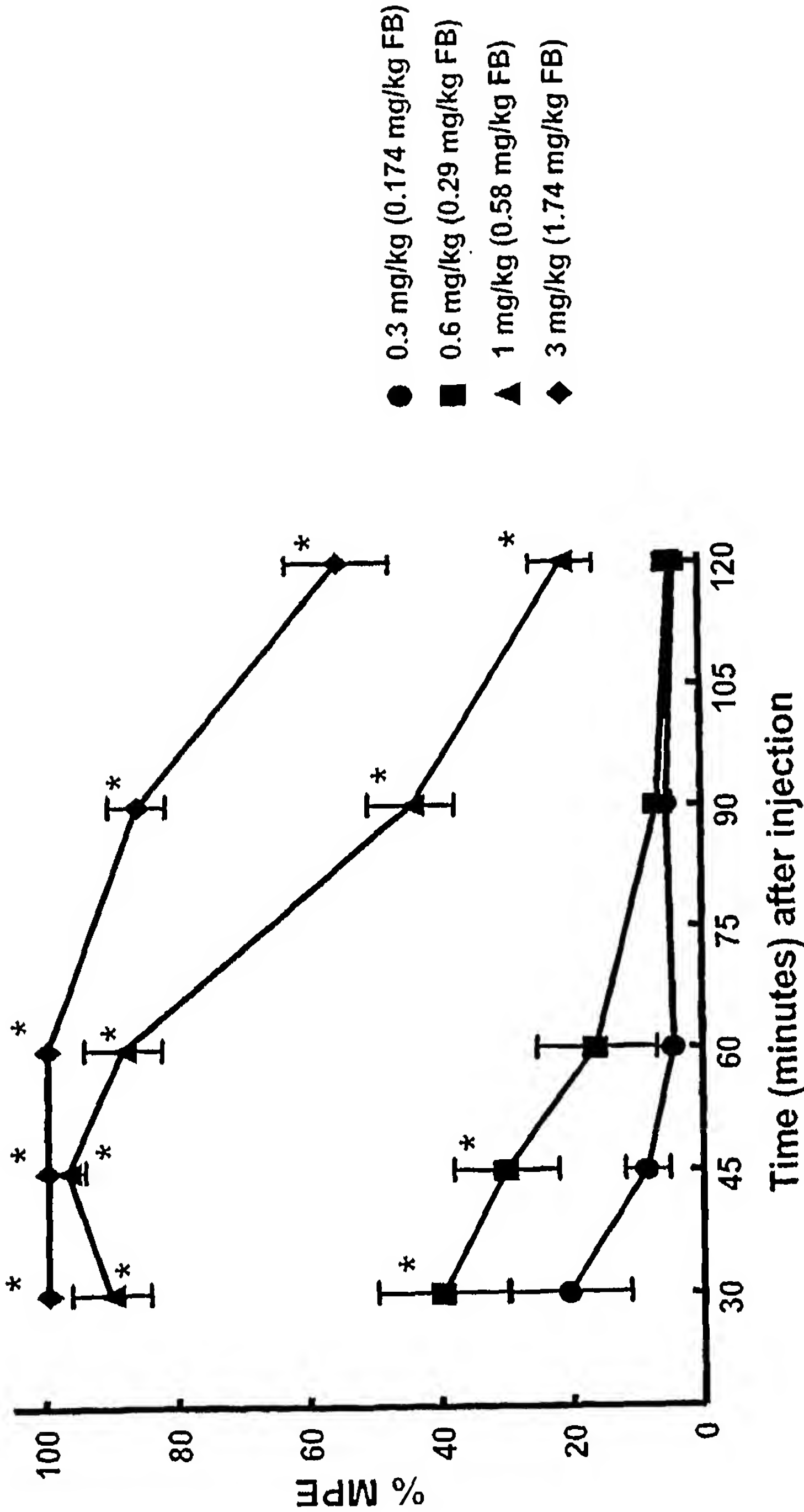


Figure 11 of 25: Antinociceptive Time-course of Levorphanol/Morphine 1:1
Fixed Ratio (Tail-flick Test)

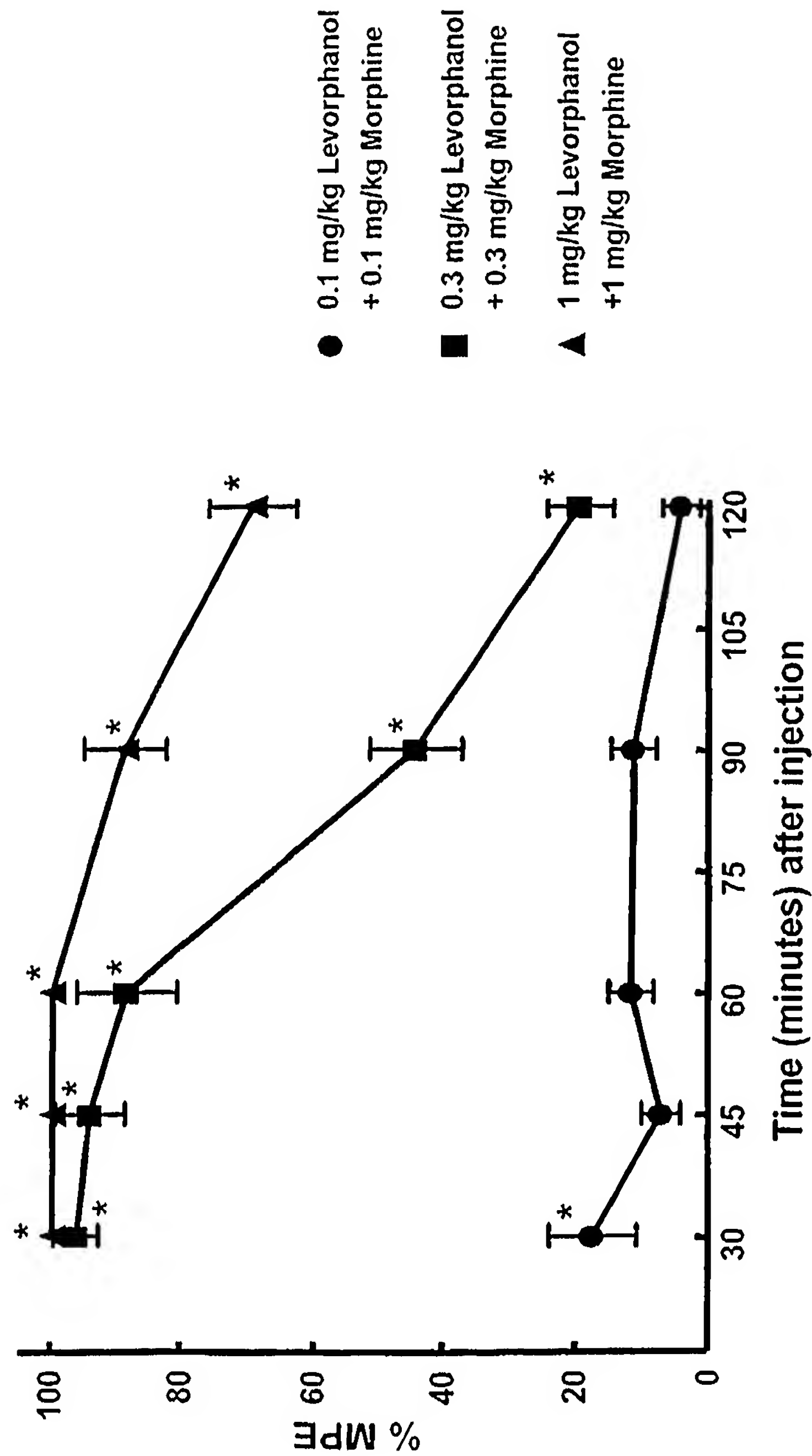


Figure 12 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 30 Minutes (Hot-plate Test)

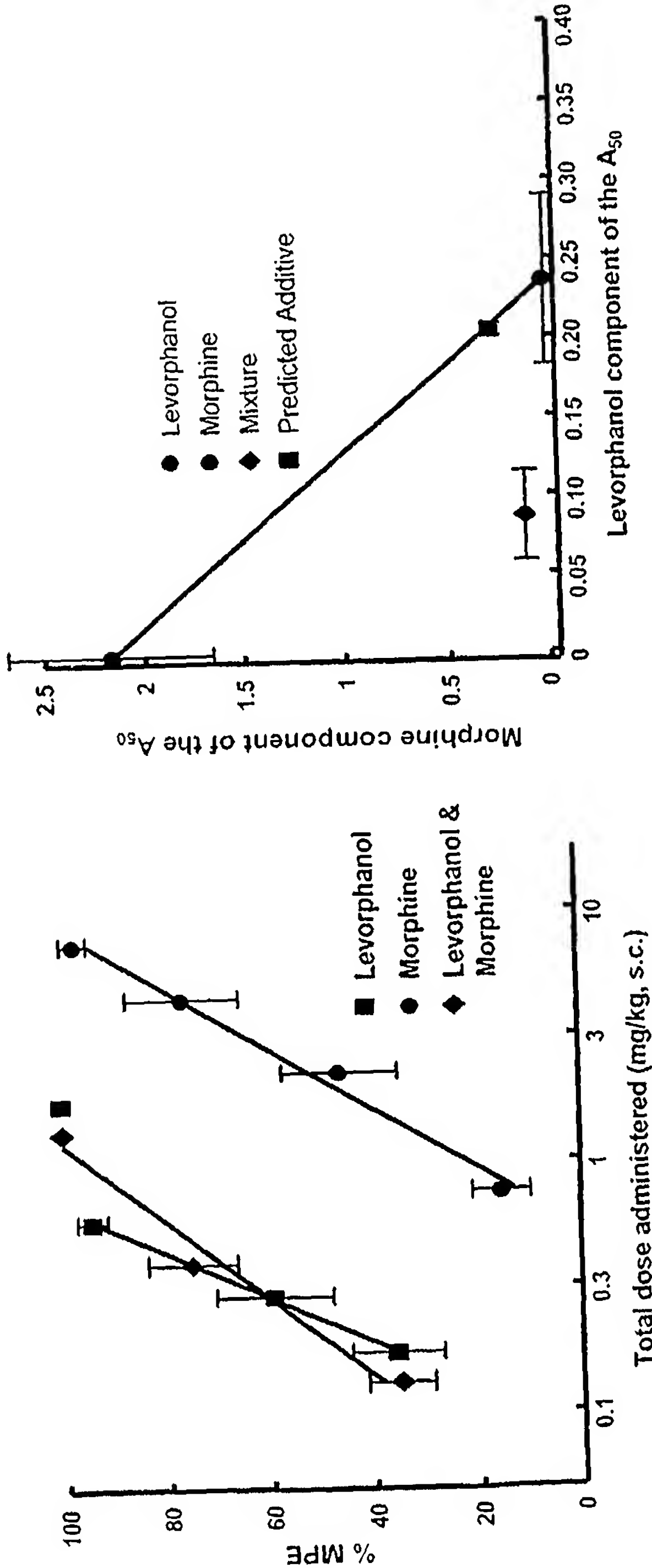


Figure 13 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 45 Minutes (Hot-plate Test)

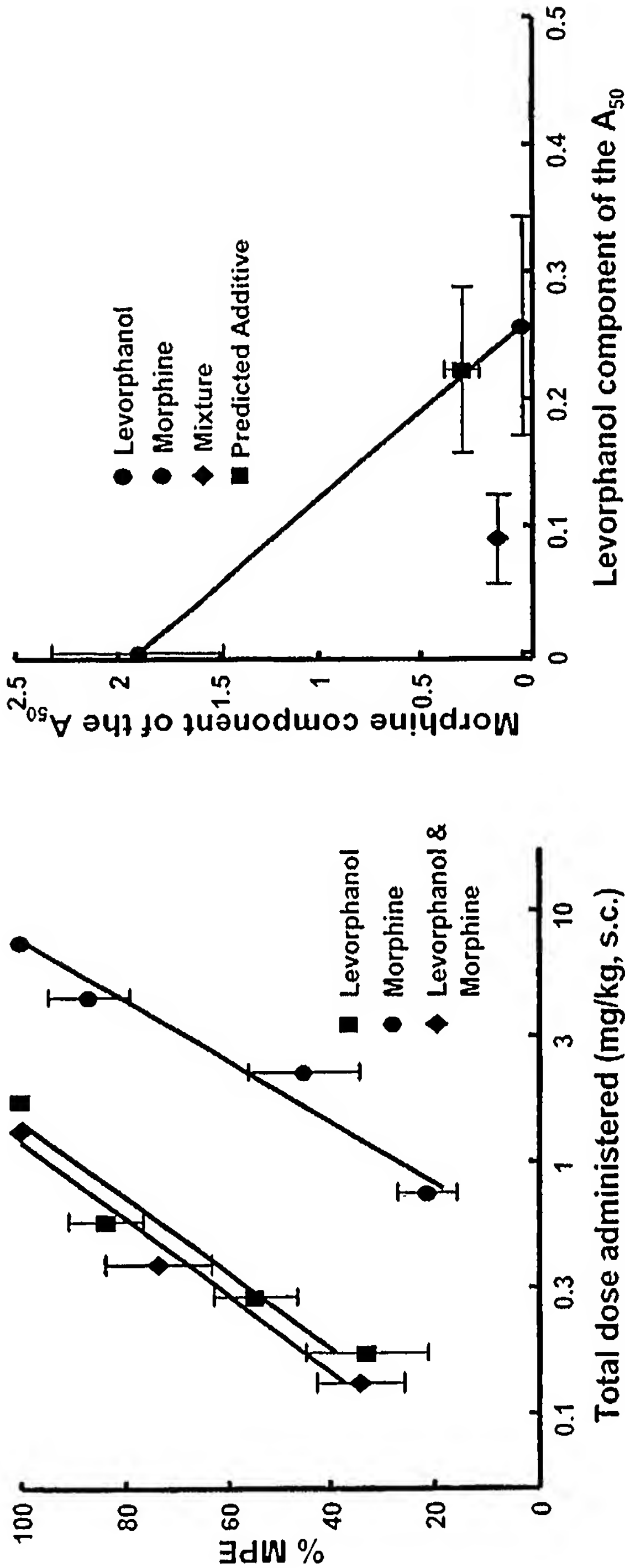


Figure 14 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 60 Minutes (Hot-plate Test)

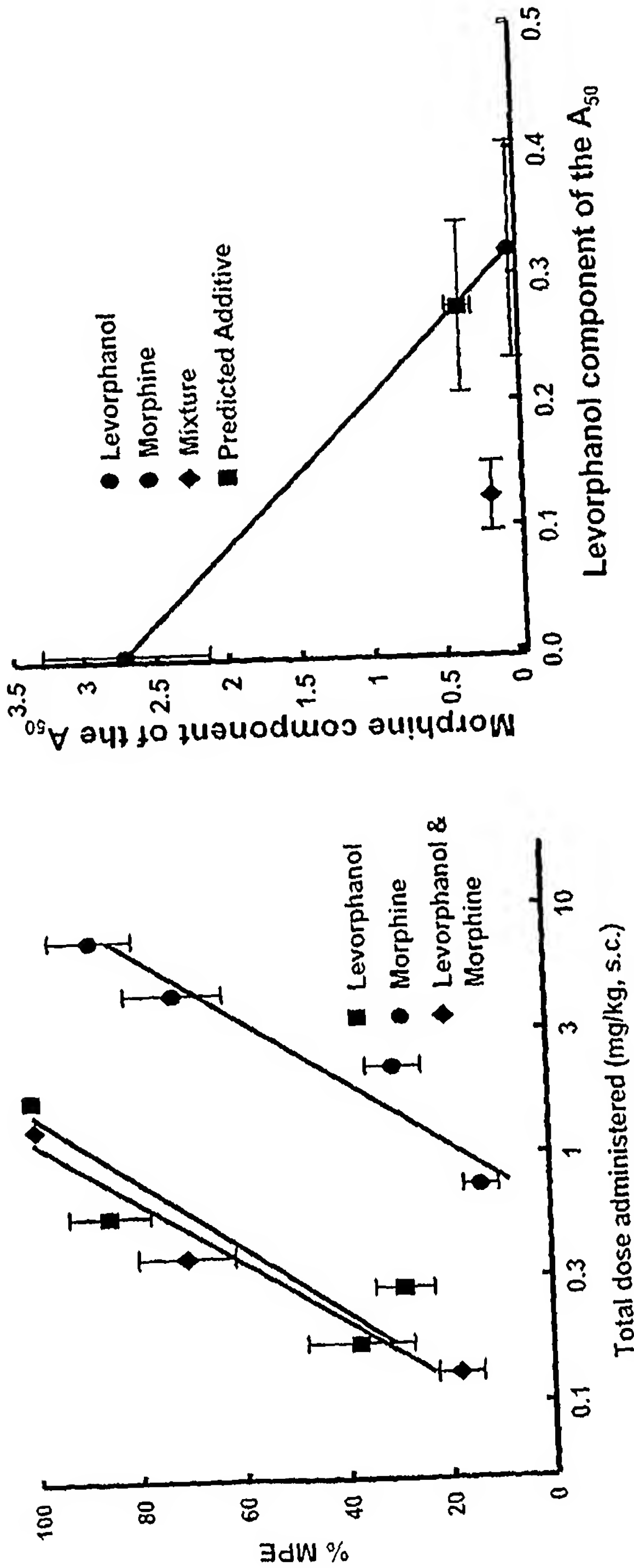


Figure 15 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 90 Minutes (Hot-plate Test)

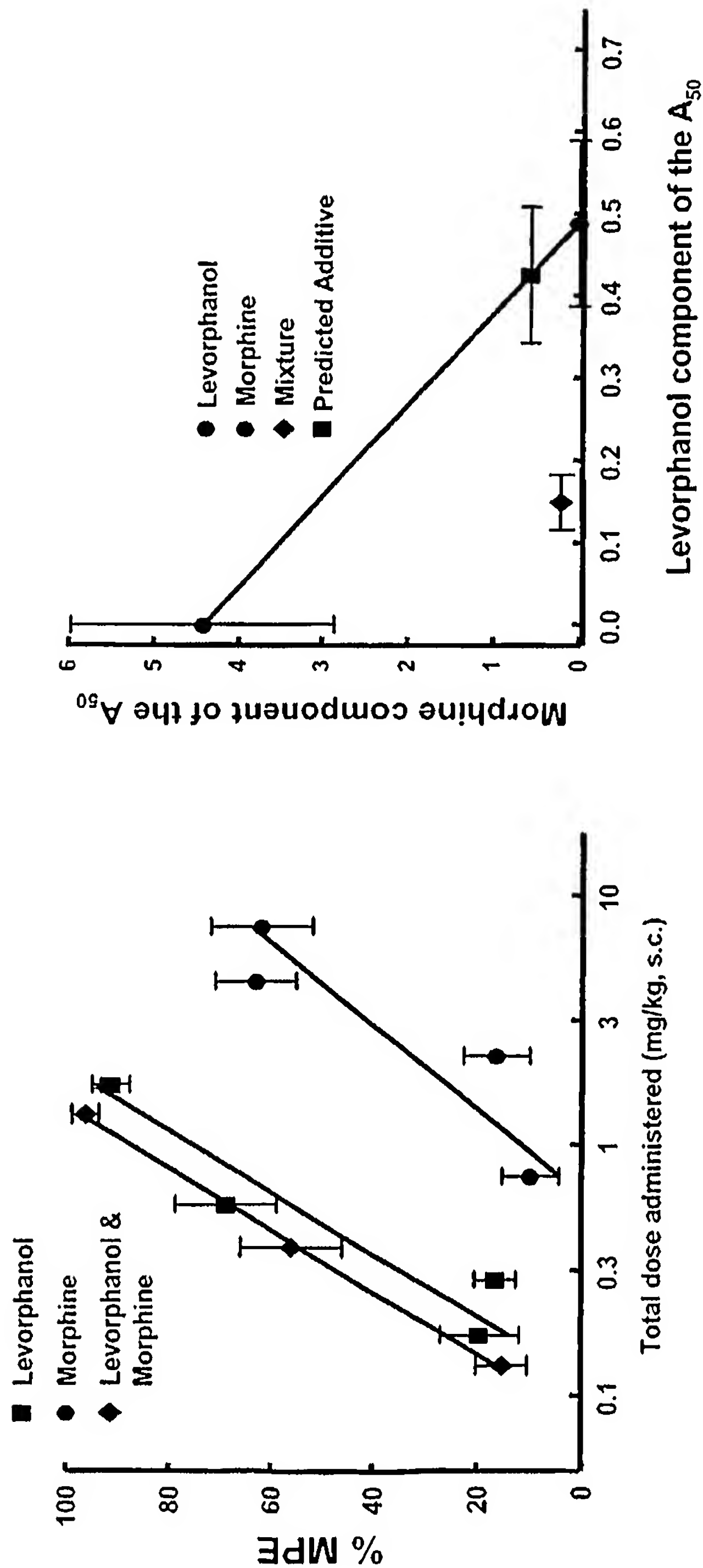


Figure 16 of 25: Antinociceptive Dose-Response Curves and Isobolograms for Levorphanol and Morphine at 120 Minutes (Hot-plate Test)

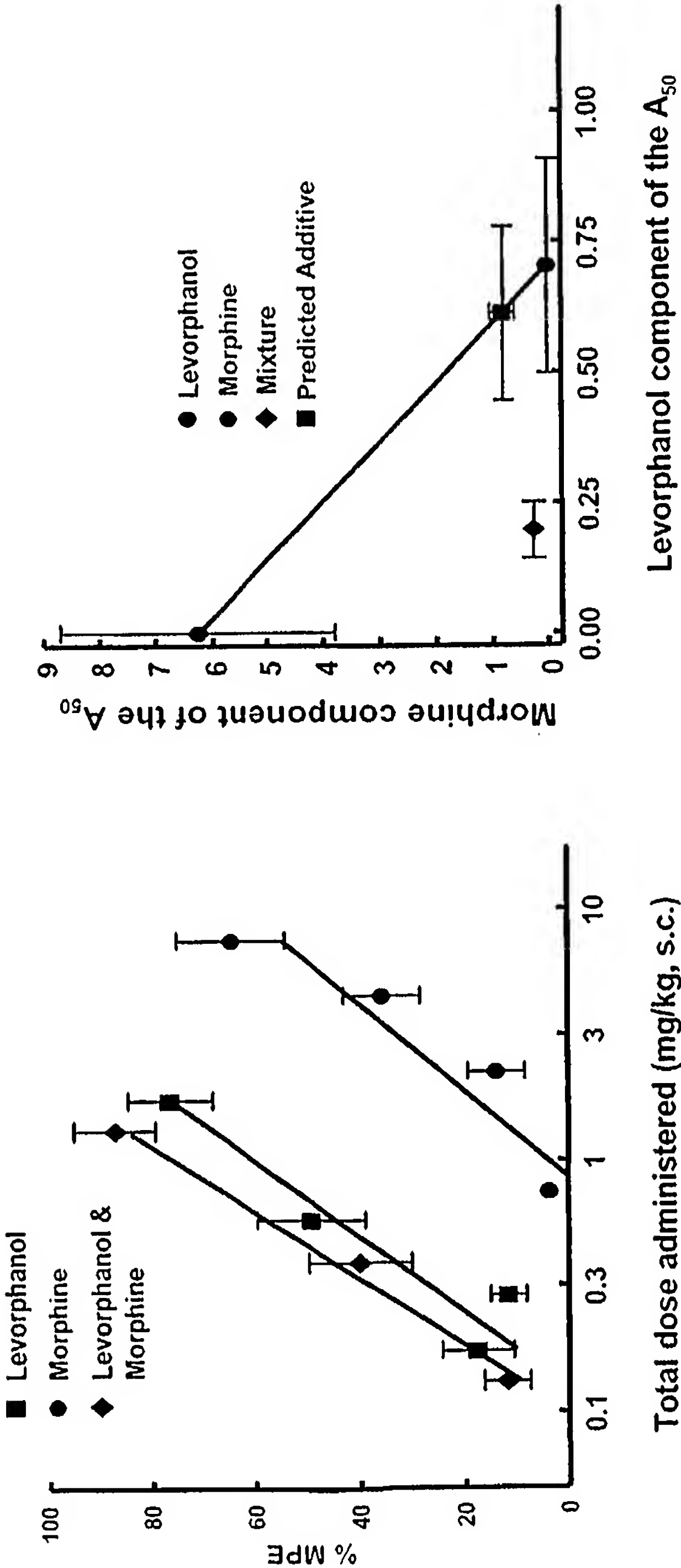


Figure 17 of 25: Antinociceptive Time-course of Low Doses of Levorphanol and Morphine
(Hot-plate Test)

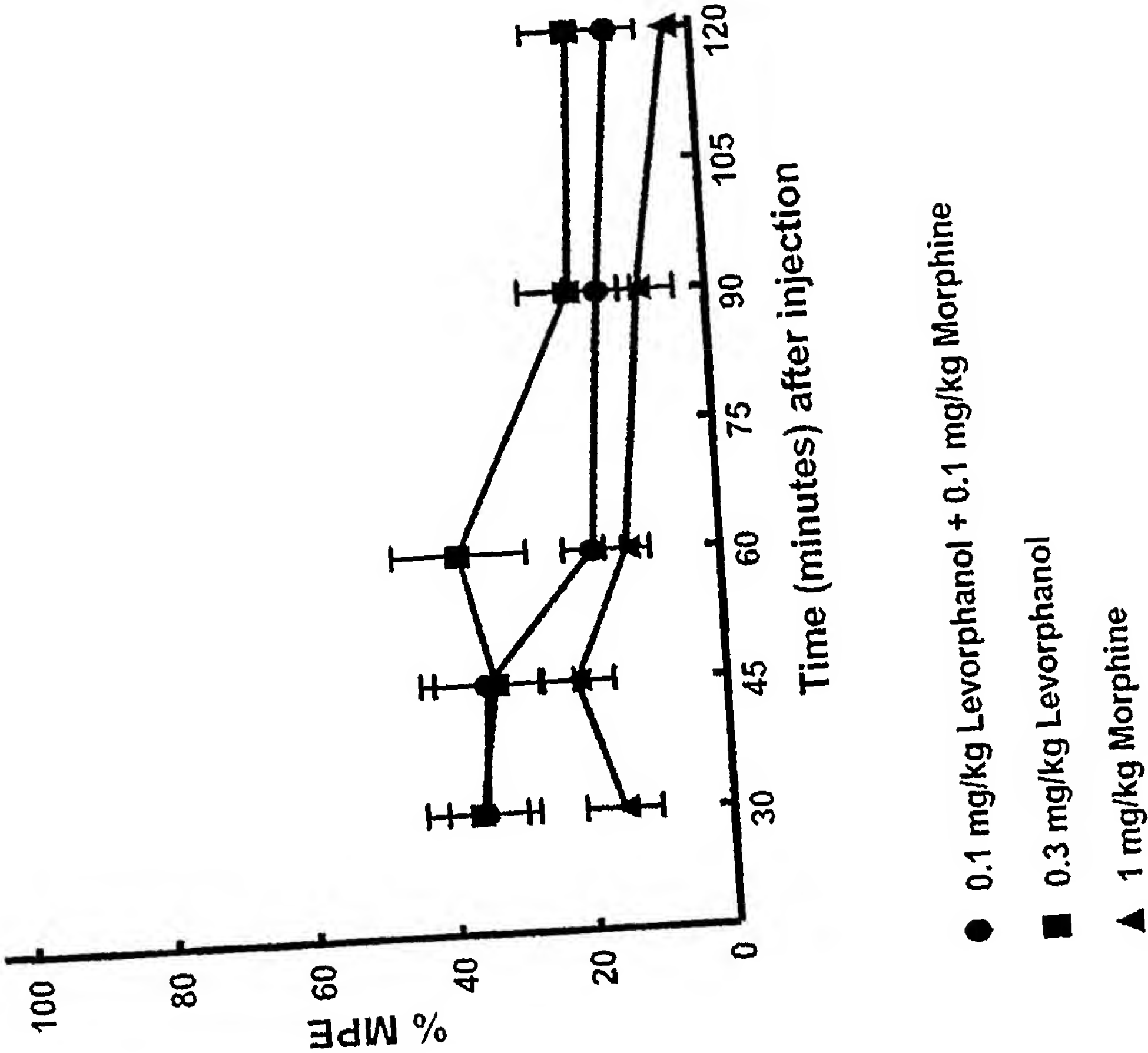


Figure 18 of 25: Antinociceptive Time-course of Intermediate Doses of Levorphanol and Morphine (Hot-plate Test)

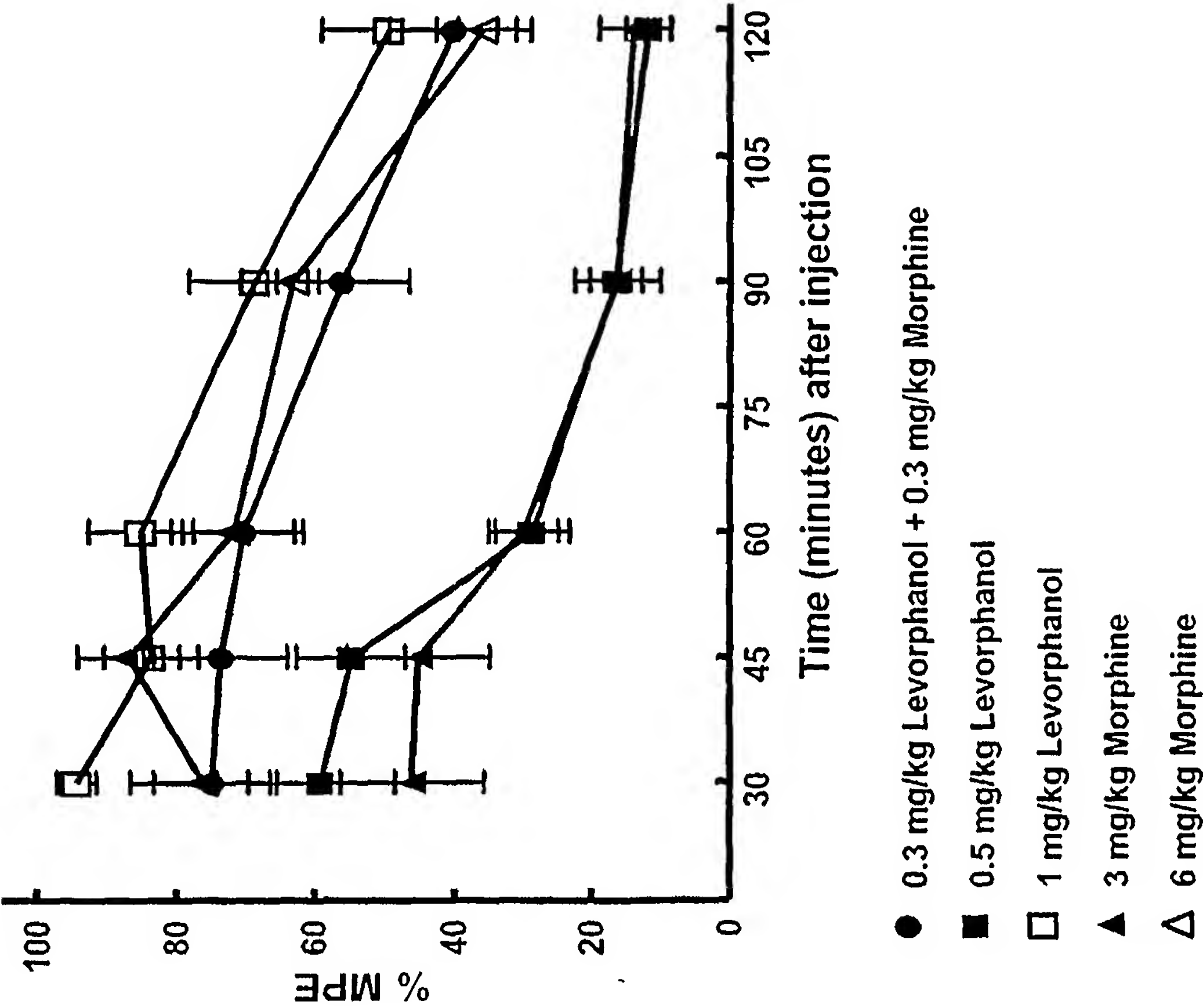


Figure 19 of 25: Antinociceptive Time-course of High Doses of Levorphanol and Morphine (Hot-plate Test)

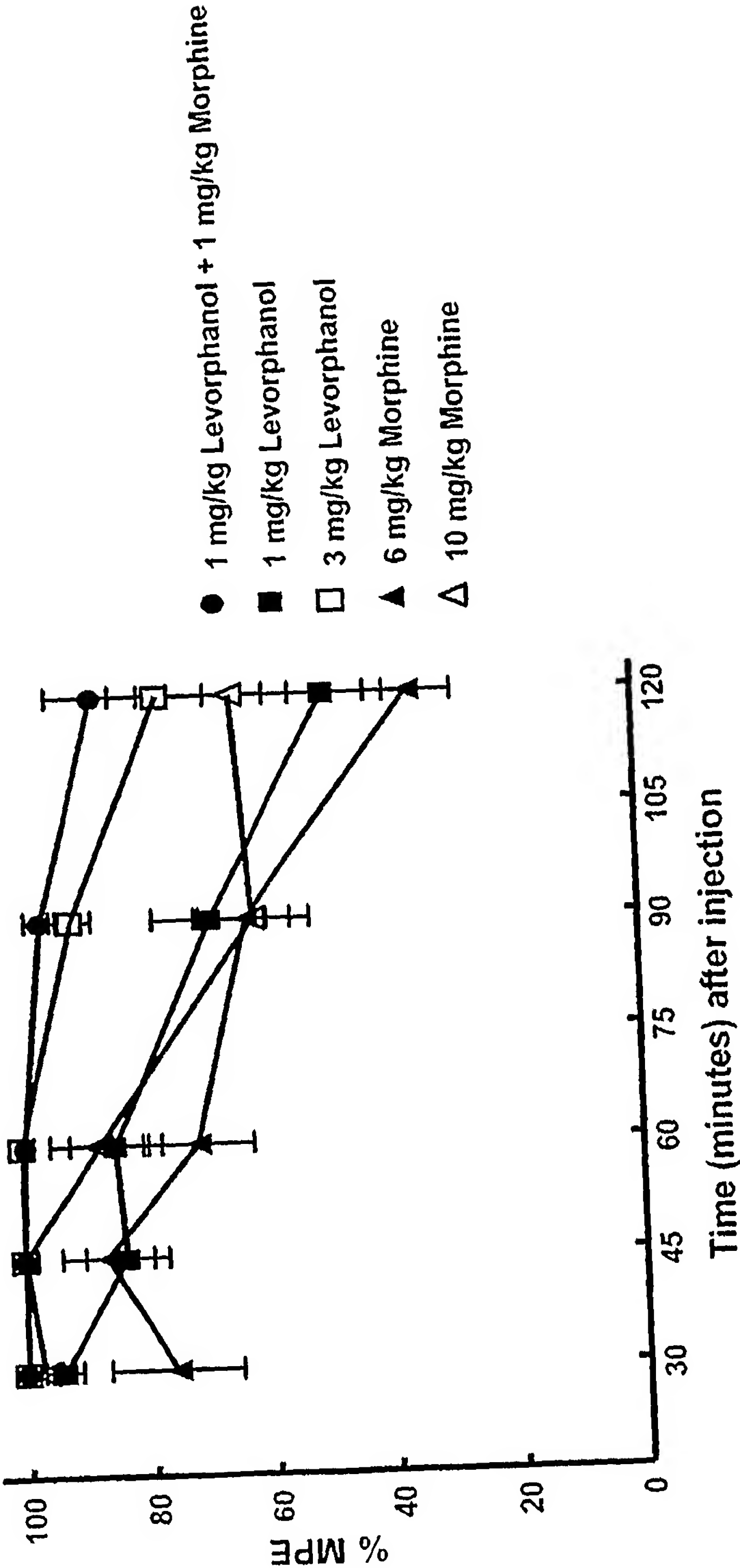


Figure 20 of 25: Antinociceptive Time-course of Morphine (Hot-plate Test)

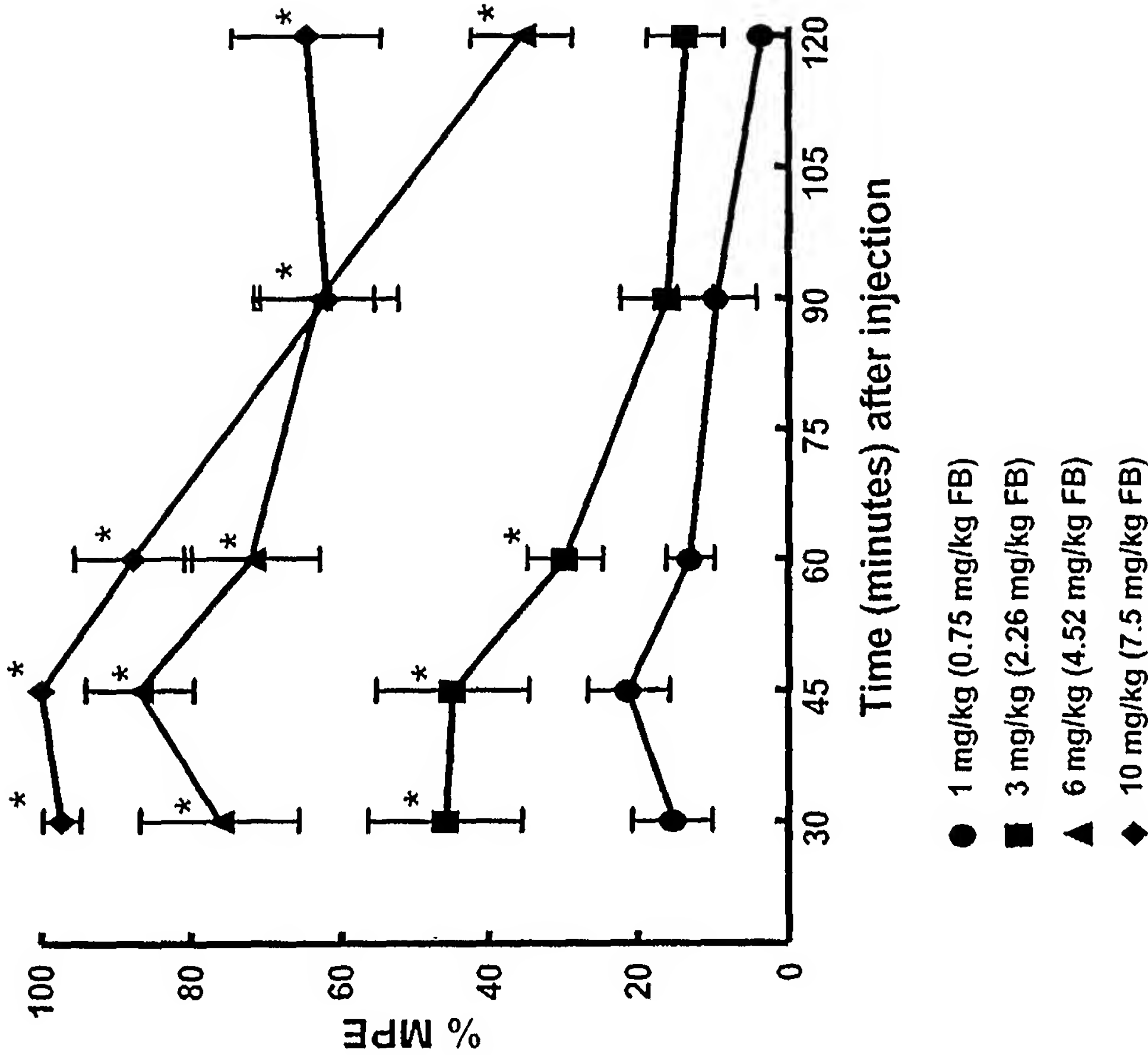


Figure 21 of 25: Antinociceptive Time-course of Levorphanol (Hot-plate Test)

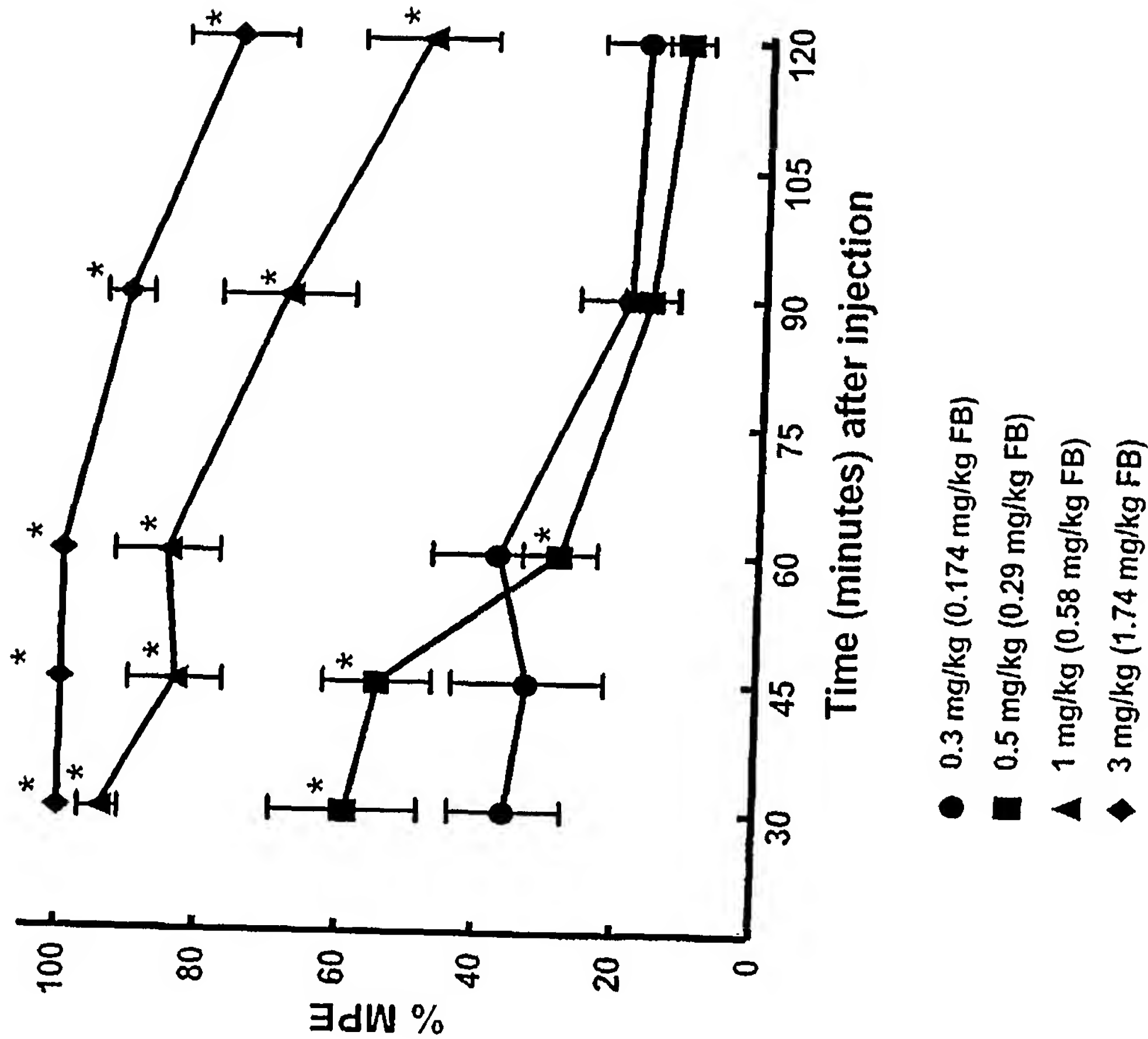


Figure 22 of 25: Antinociceptive Time-course of Levorphanol/Morphine 1:1 Fixed Ratio
(Hot-plate Test)

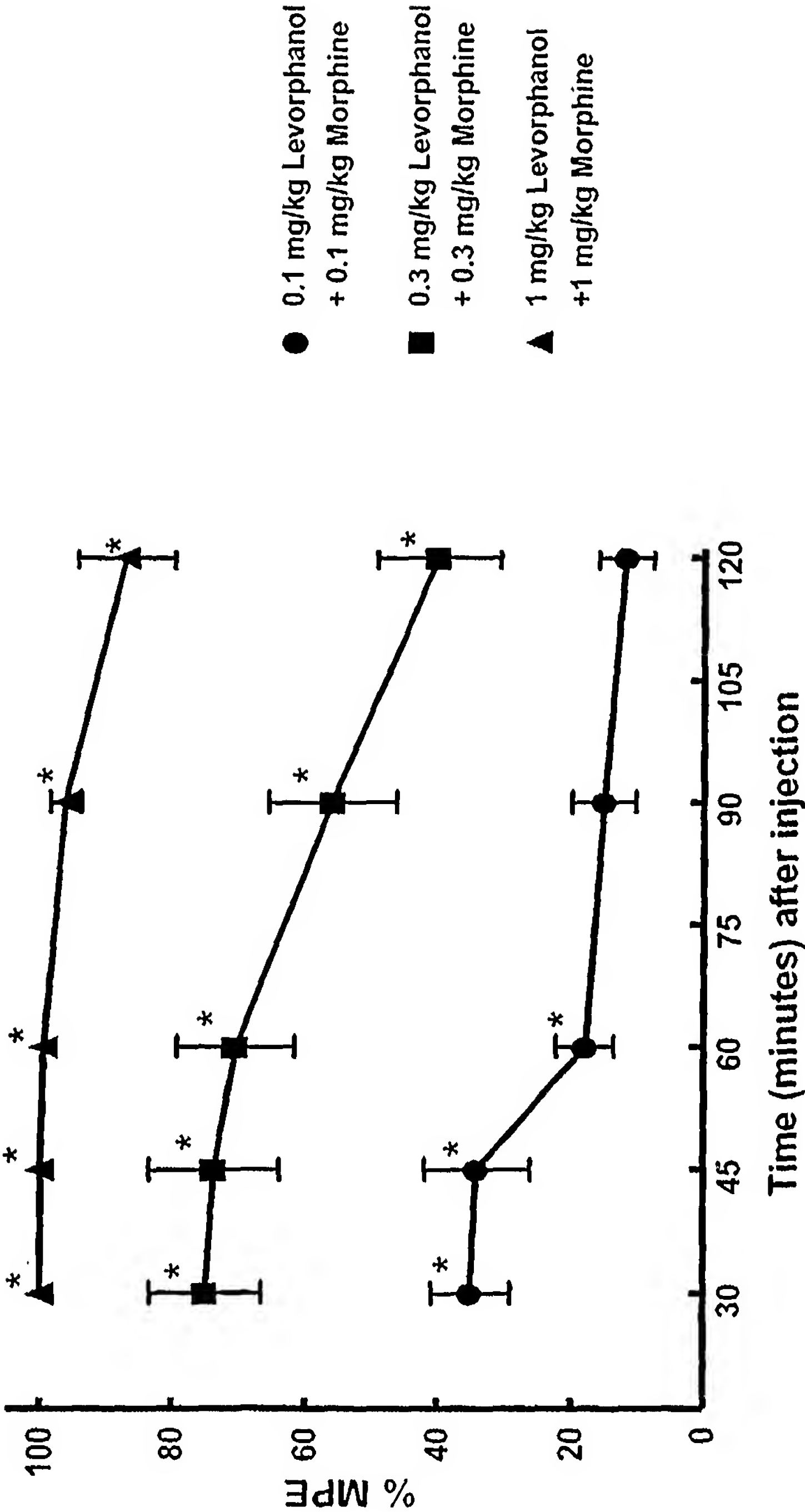


Figure 23 of 25: Antinociceptive Time-course of Fentanyl vs. Fentanyl plus Levorphanol (Tail-flick Test)

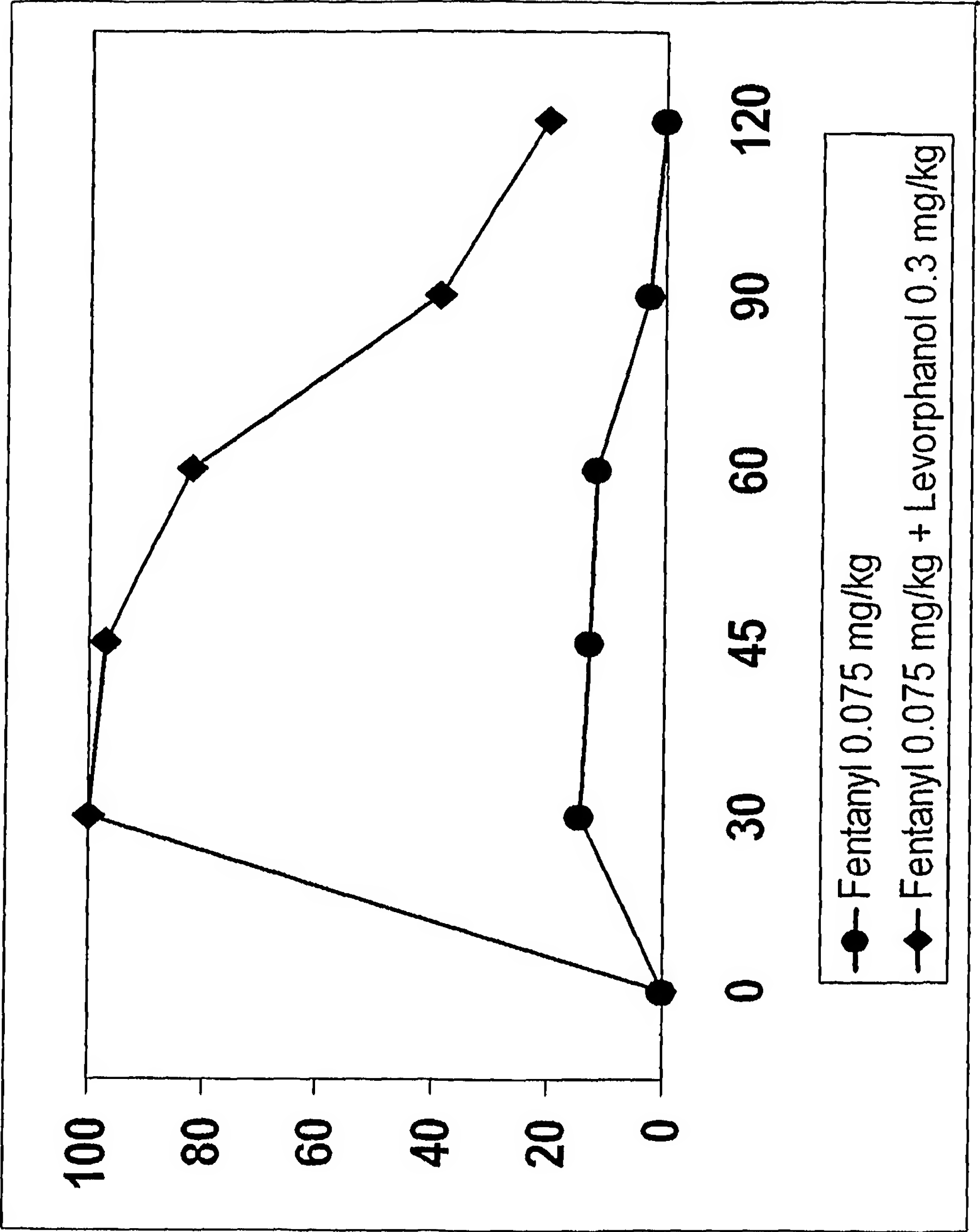


Figure 24 of 25: Antinociceptive Time-course of Hydromorphone vs. Hydromorphone + Levorphanol (Tail-flick Test)

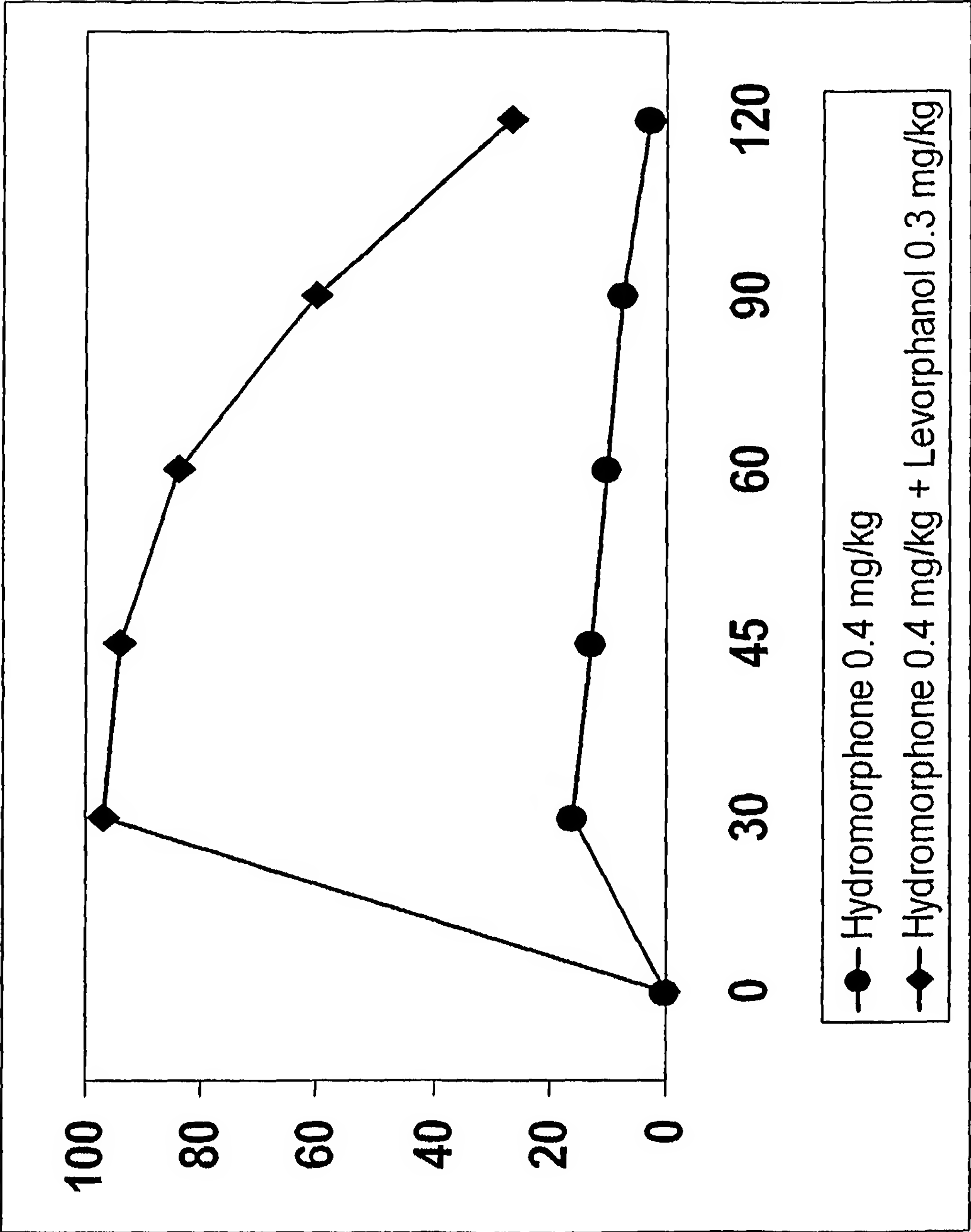


Figure 25 of 25: Antinociceptive Time-course of Oxycodone vs. Oxycodone + Levorphanol (Tail-flick Test)

